KESTREL and KITE: 52-Week Results From Two Phase III Pivotal Trials of Brolucizumab for Diabetic Macular Edema

DAVID M. BROWN, ANDRÉS EMANUELLI, FRANCESCO BANDELLO, JOSE JUAN ESCOBAR BARRANCO, JOÃO FIGUEIRA, ERIC SOUIED, SEBASTIAN WOLF, VISHALI GUPTA, NOR FARIZA NGAH, GERALD LIEW, RAMAN TULI, RAMIN TADAYONI, DILSHER DHOOT, LIXIN WANG, EMMANUEL BOUILLAUD, YING WANG, LIDIJA KOVACIC, NICOLAS GUERARD, AND JUSTUS G. GARWEG

• PURPOSE: To compare the efficacy and safety of brolucizumab with aflibercept in patients with diabetic macular edema (DME).

• DESIGN: Double-masked, 100-week, multicenter, active-controlled, randomized trials.

• METHODS: Subjects were randomized 1:1:1 to brolucizumab 3 mg/6 mg or aflibercept 2 mg in KESTREL ($n = 566$) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg in KITE ($n = 360$). Brolucizumab groups received 5 loading doses every 6 weeks (q6w) followed by 12-week (q12w) dosing, with optional adjustment to every 8 weeks (q8w) if disease activity was identified at predefined assessment visits; aflibercept groups received 5 doses every 4 weeks (q4w) followed by fixed q8w dosing. The primary endpoint was best-corrected visual acuity (BCVA) change from baseline at Week 52; secondary endpoints included the proportion of subjects maintained on q12w dosing, change in Diabetic Retinopathy Severity Scale score, and anatomical and safety outcomes.

• RESULTS: At Week 52, brolucizumab 6 mg was noninferior (NI margin 4 letters) to aflibercept in mean change in BCVA from baseline (KESTREL: +9.2 letters vs +10.5 letters; KITE: +10.6 letters vs +9.4 letters; $P < .001$), more subjects achieved central subfield thickness (CSFT) <280 µm, and fewer had persisting subretinal and/or intraretinal fluid vs aflibercept, with more than half of brolucizumab 6 mg subjects maintained on q12w dosing after loading. In KITE, brolucizumab 6 mg showed superior improvements in change of CSFT from baseline over Week 40 to Week 52 vs aflibercept ($P = .001$). The incidence of ocular serious adverse events was 3.7% (brolucizumab 3 mg), 1.1% (brolucizumab 6 mg), and 2.1% (aflibercept) in KESTREL; and 2.2% (brolucizumab 6 mg) and 1.7% (aflibercept) in KITE.

• CONCLUSION: Brolucizumab 6 mg showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME. (Am J Ophthalmol 2022;238: 157–172. © 2022 Novartis Pharma AG, Basel, Switzerland. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

AJO.com Supplemental Material available at AJO.com.

Accepted for publication January 3, 2022.

Retina Consultants of Texas, Houston, TX, USA (D.M.B); Emanuelli Research and Development Center, Arecibo, Puerto Rico, USA (A.E); Department of Ophthalmology, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico (A.E); Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy (F.B); Department of Ophthalmology, Hospital Dos de Maig, Barcelona, Spain (J.J.E.B); AIBILI - Association for Innovation and Biomedical Research on Light and Image, Azinhaga de Santa Comba, Celas, Coimbra, Portugal (J.F); Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (iCBR), University of Coimbra, Coimbra, Portugal (J.F); Department of Ophthalmology, Hôpital Intercommunal de Creteil, Créteil, France (E.S); Department of Ophthalmology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (S.W, J.G.G); Advanced Eye Center, Post Graduate Institute of Medical Education and Research, Chandigarh, India (V.G); Hospital Shah Alam, Selangor, Malaysia (N.F.N); Centre for Vision Research, Westmead Institute for Medical Research, University of Sydney, Sydney, Australia (G.L); Department of Ophthalmology, University of Ottawa, Ottawa, Canada (R.T); The Retina Centre of Ottawa, Canada (R.T); Université de Paris, Ophthalmology Department, AP-HP, Lariboisière, Saint Louis and Fondation Adolphe de Rothschild Hospitals, Paris, France (R.T); California Retina Consultants/Retina Consultants of America, Santa Barbara, CA, USA (D.D); Novartis Pharma AG, Basel, Switzerland (L.W, E.B, Y.W, L.K, N.G); Berner Augenklinik am Lindenhofspital and Swiss Eye Institute, Bern, Switzerland (J.G.G)

Inquiries to David M. Brown, Retina Consultants of Texas (Retina Consultants of America), 4360 Bissonnet, Houston TX 7700, USA.; e-mail: dmbmd@retinaconsultantstexas.com

INTRODUCTION

Diabetic macular edema (DME) is a common microvascular complication in patients with diabetes, and has become the leading cause of vision loss in the adult working population.[1,2] In the diabetic retina, hyperglycemia and oxidative stress trigger an upregulation of vascular endothelial growth factor (VEGF), lead-

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2022.01.004

ing to a breakdown of the inner blood-retinal barrier and increased vascular permeability.[3,4] Subsequent fluid leakage into the intraretinal layers causes swelling or thickening of the macula characteristic of DME and compromises visual function.[3,4]

Following the Phase III trials RESTORE[5] and RISE/RIDE[6,7] with ranibizumab (Lucentis, Genentech, South San Francisco, California, USA) and VIVID/VISTA[8,9] with aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA), anti-VEGF therapy replaced focal/grid laser photocoagulation as the first-line therapy for DME.[10] However, despite the overall anatomical and functional improvements achieved with anti-VEGF treatment, some patients continue to have persistent DME, despite continuous therapy. The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared 3 treatments for DME—intravitreous aflibercept 2 mg, bevacizumab 1.25 mg, and ranibizumab 0.3 mg—and reported central subfield thickness (CSFT) >250 μm in 29% of eyes receiving aflibercept, 59% receiving bevacizumab, and 35% receiving ranibizumab treatment after 2 years.[11] A post hoc analysis of another DRCR.net study, Protocol I, estimated that of eyes treated with 4-monthly ranibizumab injections and then *pro re nata* (PRN) with persistent DME at 24 weeks, approximately 40% will have chronic persistent DME through 3 years.[12] Furthermore, this analysis showed that visual acuity (VA) improvement from baseline to 3 years was lower in the eyes with chronic persistent DME (mean VA gain, +7 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) compared with those without (mean VA gain, +13 ETDRS letters).

With the currently available anti-VEGFs, intensive treatment is often required to dry the macula as far as possible and achieve optimal treatment outcomes.[13] However, patients with DME often experience a high medical burden due to multiple comorbidities[14] and real-world evidence shows that this can result in high rates of noncompliance, under-treatment for DME and, in turn, lower visual gains.[15,16] Further treatment options are therefore needed to improve the response rate and/or reduce treatment burden via a lower frequency of injection and monitoring visits, while maintaining visual function in patients with DME.

Brolucizumab is a single-chain antibody fragment (scFv) that has a high affinity for VEGF. Its low molecular weight (26 kDa) enables delivery of more drug per injection compared with other available anti-VEGFs and offers the potential for more effective tissue penetration and increased duration of action.[17] In the Phase III HAWK and HARRIER trials, brolucizumab 6 mg demonstrated comparable best-corrected visual acuity (BCVA) gains and superior anatomical outcomes compared with aflibercept in subjects with neovascular age-related macular degeneration (nAMD), with >50% of subjects maintained on every 12 week (q12w) dosing after the loading phase to Week 48.[18,19] The current study reports the primary 52-week outcomes of KESTREL and KITE studies to evaluate the efficacy and safety of brolucizumab in the treatment of patients with visual impairment due to DME.

METHODS

• **STUDY DESIGN:** KESTREL (NCT03481634) and KITE (NCT03481660) are 2 Phase III, 100-week, randomized, double-masked, active-controlled, multicenter trials. The KESTREL study was conducted across 118 sites in the USA, Europe, Canada, Latin America, Japan, Australia, and Israel, whereas KITE was conducted at 79 sites in Europe, Asia, and Russia (a list of principal investigators of both studies is provided in **Appendix 1**). Protocols were approved by an Independent Ethics Committee/Institutional Review Board for each center. Trials were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guideline, and other regulations. All subjects provided written informed consent prior to screening or initiation of any study-related procedures. The primary 52-week outcomes contained within this report were collected between July 2018 and November 2020.

• **STUDY POPULATION:** Eligible participants were aged ≥18 years with type 1 or 2 diabetes mellitus, glycosylated hemoglobin (HbA1c) ≤10%, and who presented with (i) BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline; and (ii) central-involved DME with CSFT of ≥320 μm on spectral domain optical coherence tomography (SD-OCT) at screening. Only 1 eye per subject was included in the study. Subjects were excluded if they had active proliferative diabetic retinopathy in the study eye, had received intraocular or periocular corticosteroids in the 6 months prior to baseline, or prior anti-VEGF therapy at any time in the study eye. Full inclusion/exclusion criteria are provided in **Appendix 2**.

• **RANDOMIZATION AND TREATMENT:** Eyes were randomized 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg (KESTREL), or 1:1 to brolucizumab 6 mg or aflibercept 2 mg (KITE). Following 5 loading doses every 6 weeks (5xq6w, Weeks 0, 6, 12, 18, and 24) in the brolucizumab arms, the study eyes were given an intravitreal injection every 12 weeks (q12w) with the option of adjusting the dose to every 8 weeks (q8w) for the remainder of this study period if disease activity (e.g. ≥ 5 letters loss in BCVA with increase in CSFT compared with the subject's disease status at Week 28) was detected at any of the predefined assessment visits; aflibercept study eyes received 5

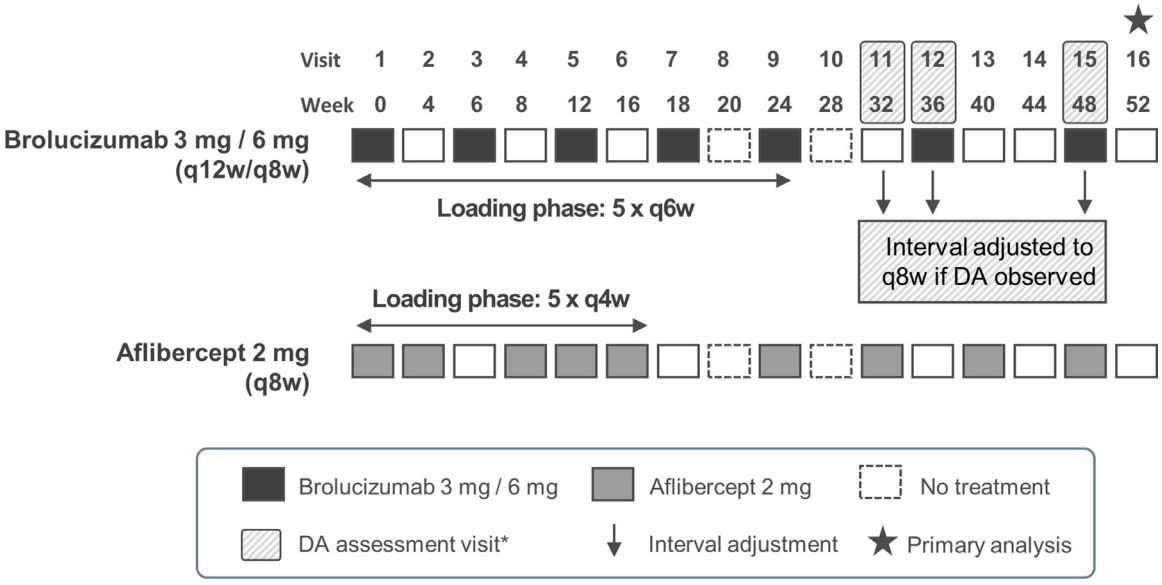

FIGURE 1. KESTREL and KITE study design. *Disease activity assessments were conducted at prespecified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to all injections. DA = disease activity, q8w = 8-week dosing interval, q12w = 12-week dosing interval.

monthly loading doses (5xq4w, Weeks 0, 4, 8, 12 and 16), followed by fixed q8w, as per label[20] (Figure 1). For masking purposes, all subjects underwent disease activity assessments (DAAs) by the masked investigator at Weeks 32, 36, and 48 in the first year; a 'q8w treatment need' was identified if disease activity was detected in eyes at any of these visits. Aflibercept-treated eyes received q8w dosing regardless of the outcome of these DAAs, but the masked investigators made the final treatment decision based on their own clinical judgement for brolucizumab-treated eyes. The trials were double-masked. Subjects, investigators, and site personnel were masked from treatment until the end of the study, except in the case of emergencies. The unmasked injecting investigator and site personnel did not perform BCVA, complete pre-injection ophthalmic examinations, DAAs or administer the Visual Function Questionnaire 25 (VFQ-25) assessment. To maintain masking, aflibercept-treated eyes underwent the same DAAs as brolucizumab-treated eyes, and sham injections were performed when study treatments were administered at different time points. Further details on randomization and masking are included in Appendix 3.

• **ENDPOINTS:** The primary endpoint was mean BCVA change from baseline at Week 52. The first key secondary endpoint was BCVA change from baseline averaged over the period of Week 40 through Week 52 (to account for differences in timing of treatment), and other secondary endpoints were q12w treatment status at Week 52 (brolucizumab only), and q12w treatment status at Week 52 among eyes with no q8w need during the first q12w cycle (to evaluate the predictive value of the first q12w cycle; brolucizumab only). Additional secondary efficacy endpoints included, for each post-baseline visit, changes from baseline in BCVA (including BCVA gain/loss of ≥ 15 letters) and CSFT, status of subretinal fluid (SRF)/intraretinal fluid (IRF), percentage of subjects with CSFT <280 µm at Week 52, and change in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score from baseline. Safety endpoints included incidence of ocular and non-ocular adverse events.

• **STUDY ASSESSMENTS:** The following assessments were performed to evaluate the effect of brolucizumab and aflibercept on visual function and anatomical outcomes: BCVA with ETDRS chart at an initial testing distance of 4 meters (every 4 weeks); anatomical markers on SD-OCT (every 4 weeks); ETDRS DRSS score based on 7-field stereo color fundus photography (at screening, Week 28 and Week 52); and vascular leakage evaluation by fluorescein angiography (at screening, Week 28 and Week 52). An independent, masked review of fundus photography, fluorescein angiography, and OCT images was performed by a Central Reading Center (CRC) to ensure a standardized evaluation. Grading for DRSS was also performed at the CRC. Further details on efficacy and safety assessments are included in Appendix 4.

• **STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION:** Primary and key secondary endpoints were analyzed

based on the full analysis set (FAS) with ANOVA model including terms for treatment, baseline BCVA (≤65, >65 letters), and age category (<65, ≥65 years), and using last observation carried forward (LOCF) imputation/replacement for missing/censored data. Two-sided 95% confidence intervals (CIs) for the least square (LS) mean difference (brolucizumab - aflibercept) are presented in letters. Non-inferiority was considered established if the lower limit of the corresponding 95% CI was > –4 letters. The *P*-value for non-inferiority (1-sided) is presented. All other secondary endpoints were summarized descriptively, based on the FAS with LOCF imputation for missing data and LOCF replacement for censored data, if not otherwise specified. Safety endpoints were based on the safety set (SAF) and analyzed descriptively.

If each BCVA-related noninferiority hypothesis (**Appendix 5**). reached statistical significance, additional confirmatory superiority testing of brolucizumab vs aflibercept was prespecified, with hierarchical testing in the categories of average change from baseline in CSFT over the period Weeks 40 through 52, average change from baseline in BCVA over the period Weeks 40 through 52, and presence of IRF and/or SRF at Week 52. Confirmatory testing of the hypothesis required rejection of the previous null hypothesis and each hypothesis was assessed at a 1-sided significance level of 0.025, while keeping the global type I error rate at 0.025. The probabilities for maintaining q12w status were derived from time-to-event analyses (first disease activity/q8w-need). In case of informative censoring (lack of efficacy or safety), q8w need was imputed. Data from both KESTREL and KITE studies were pooled to support overall conclusions regarding the non-inferior efficacy of brolucizumab 6 mg compared with aflibercept 2 mg in terms of ≥ 2 steps improvement in DRSS score with a 10% non-inferiority margin (see **Appendix 5** for the multiple testing procedure used).

A sample size of 160 eyes per arm allowed non-inferiority determination of brolucizumab 3 mg or 6 mg vs aflibercept regarding BCVA change from baseline to Week 52 at a 1-sided alpha level of 0.025 with a power of approximately 90%, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points would not lead to an increase in the standard deviation, a power of at least 90% could also be expected for its corresponding non-inferiority claim. Considering a drop-out rate of 10%, approximately 178 subjects per treatment arm were planned to be randomized.

RESULTS

• **SUBJECT DISPOSITION:** In the KESTREL study, of a total of 873 subjects were screened, and 566 subjects were randomized in a 1:1:1 ratio to the brolucizumab 6 mg ($n = 189$), brolucizumab 3 mg ($n = 190$), or aflibercept 2 mg arm ($n = 187$) between 30 July 2018 and 14 November 2019. Of a total of 480 subjects who were screened in the KITE study, 360 subjects were randomized in a 1:1 ratio to the brolucizumab 6 mg ($n = 179$) or aflibercept 2 mg arm ($n = 181$) between 10 August 2018 and 02 July 2019. Subject disposition details are shown in Supplementary Figure 1.

• **BASELINE CHARACTERISTICS:** Baseline demographic and disease characteristics were generally similar across treatment groups in both trials (Table 1). In total, there were more males (KESTREL: 62.7%; KITE: 65.3%) than females (KESTREL: 37.3%; KITE: 34.7%) in the study, with comparable proportions between the treatment arms. Mean baseline BCVA in KITE was slightly higher for the brolucizumab 6 mg arm vs the aflibercept arm (66.0 vs 63.7 letters, respectively). Almost all subjects (98.3% to 100%) showed presence of IRF at baseline in both KITE and KESTREL, whereas SRF was present in 31.3% to 37.0% of subjects across all treatment arms.

• **BEST-CORRECTED VISUAL ACUITY:** The studies met their primary objective and demonstrated non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the primary endpoint of change from baseline in BCVA at Week 52 for the study eye, with a non-inferiority margin of 4 letters ($P < .001$). The LS mean estimate was +9.2 letters in the brolucizumab 6 mg arm compared with +10.5 letters in the aflibercept arm, with a difference of −1.3 letters (95% CI: [−2.9, 0.3]), after adjustment for baseline BCVA categories and age categories, in the KESTREL study (Figure 2**A**). Non-inferiority of brolucizumab 3 mg to aflibercept was not achieved ($P = .227$). In KITE, the LS mean estimate was +10.6 letters in the brolucizumab 6 mg arm compared with +9.4 letters in the aflibercept arm, with a difference of 1.2 letters (95% CI: [−0.6, 3.1]) after adjustment for baseline BCVA categories and age categories (Figure 2B).

The proportion of subjects who gained ≥ 15 letters from baseline in BCVA or reached BCVA of ≥ 84 letters in the KESTREL study was lower in the brolucizumab 3 mg arm compared with the aflibercept arm (34.2% vs 39.0%, respectively) but generally comparable between the brolucizumab 6 mg arm and the aflibercept arm (37.0% vs 39.0%, respectively; Figure 2C). This proportion was generally higher in the brolucizumab 6 mg arm at Week 52 compared with the aflibercept arm (46.4% vs 37.6%, respectively) of the KITE study (Figure 2D).

Non-inferiority of brolucizumab 6 mg to aflibercept 2 mg was met for the first key secondary endpoint with average change from baseline in BCVA over the period Week 40 through Week 52 for the study eye, with a non-inferiority margin of 4 letters ($P < .001$) in both the trials (Supplementary Table 1).

TABLE 1. Subject Demographics and Baseline Disease Characteristics in KESTREL and KITE

	KESTREL			KITE	
Characteristic	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* =187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
Age (years) Mean (SD)	64.4 (9.76)	62.4 (10.14)	63.9 (10.09)	62.3 (10.55)	62.2 (9.48)
<65 years	97 (51.1)	104 (55.0)	93 (49.7)	100 (55.9)	102 (56.4)
≥65 years	93 (48.9)	85 (45.0)	94 (50.3)	79 (44.1)	79 (43.6)
Sex, *n* (%)					
Male	119 (62.6)	110 (58.2)	126 (67.4)	120 (67.0)	115 (63.5)
Race, *n* (%)					
White	151 (79.5)	158 (83.6)	153 (81.8)	133 (74.3)	132 (72.9)
Black or African American	13 (6.8)	4 (2.1)	7 (3.7)	3 (1.7)	1 (0.6)
Asian	25 (13.2)	25 (13.2)	27 (14.4)	43 (24.0)	48 (26.5)
Japanese	20 (10.5)	20 (10.6)	22 (11.8)	-	-
Indian	3 (1.6)	5 (2.6)	2 (1.1)	14 (7.8)	11 (6.1)
Chinese	2 (1.1)	0	1 (0.5)	13 (7.3)	17 (9.4)
Korean	-	-	-	9 (5.0)	10 (5.5)
Vietnamese	-	-	-	0	1 (0.6)
American Indian/Alaska Native	1 (0.5)	0	1 (0.5)	-	-
Native Hawaiian/Other Pacific Islander	0	2 (1.1)	0	-	-
Type II diabetes – m (%)	180 (94.7)	177 (93.7)	181 (96.8)	160 (89.4)	174 (96.1)
Mean HbA1c, % (SD)	7.52 (1.160)	7.69 (1.067)	7.44 (1.132)	7.55 (1.174)	7.46 (1.161)
HbA1c group, m (%)					
<7 .5%	100 (52.6)	76 (40.4)	107 (57.2)	82 (45.8)	96 (53.0)
≥7.5%	90 (47.4)	112 (59.6)	80 (42.8)	97 (54.2)	85 (47.0)
Time since DME diagnosis (months) Mean (SD)	12.5 (30.82)	9.4 (19.47)	9.6 (24.17)	10.4 (16.56)	9.9 (20.73)
BCVA (letters) Mean (SD)	65.7 (11.09)	66.6 (9.67)	65.2 (12.38)	66.0 (10.77)	63.7 (11.70)
BCVA group, m (%)					
<60 letters	44 (23.2)	36 (19.0)	41 (21.9)	42 (23.5)	50 (27.6)
≥60 to ≤70 letters	68 (35.8)	70 (37.0)	71 (38.0)	55 (30.7)	73 (40.3)
>70 letters	78 (41.1)	83 (43.9)	75 (40.1)	82 (45.8)	58 (32.0)
CSFT (μm)					
Mean (SD)	456 (118)	453 (123)	476 (136)	481 (132)	484 (135)
CSFT group, m (%)					
<450 μm	111 (58.4)	107 (56.6)	96 (51.3)	85 (47.5)	82 (45.6)
≥450 to <650 μm	64 (33.7)	70 (37.0)	71 (38.0)	74 (41.3)	79 (43.9)
≥650 μm	15 (7.9)	12 (6.3)	20 (10.7)	20 (11.2)	19 (10.6)
Intraretinal fluid, m (%) Present	190 (100)	189 (100)	184 (98.4)	176 (98.3)	179 (98.9)
Subretinal fluid, m (%) Present	60 (31.6)	62 (32.8)	61 (32.6)	56 (31.3)	67 (37.0)
Diabetic Retinopathy Severity Scale, m (%)					
n	185	186	184	176	177
1- DR absent	1 (0.5)	0	0	3 (1.7)	1 (0.6)
2- Microaneurysms only	3 (1.6)	1 (0.5)	3 (1.6)	0	2 (1.1)
3- Mild NPDR	56 (30.3)	57 (30.6)	52 (28.3)	49 (27.8)	37 (20.9)
4- Moderate NPDR	51 (27.6)	54 (29.0)	59 (32.1)	55 (31.3)	68 (38.4)
5- Moderately severe NPDR	25 (13.5)	15 (8.1)	16 (8.7)	30 (17.0)	20 (11.3)
6- Severe NPDR	39 (21.1)	45 (24.2)	40 (21.7)	26 (14.8)	34 (19.2)
7- Mild PDR	6 (3.2)	3 (1.6)	7 (3.8)	9 (5.1)	7 (4.0)
8- Moderate PDR	4 (2.2)	8 (4.3)	5 (2.7)	3 (1.7)	5 (2.8)
9- High-risk PDR	0	3 (1.6)	2 (1.1)	1 (0.6)	2 (1.1)
>10- Very high-risk PDR	0	0	0	0	0

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	KESTREL			KITE	
	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* =187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
11- Advanced PDR	0	0	0	0	1 (0.6)
12- Very advanced PDR	0	0	0	0	0

Abbreviations: BCVA = best corrected visual acuity, BL = baseline, CSFT = central subfield thickness, DR = diabetic retinopathy, HbA1c = glycosylated hemoglobin A1c, m = number of subjects with assessment meeting the criterion for the given categorical variables, *n* = number of subjects with an assessment, *N* = total number of subjects, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, Q = quartile, SD = standard deviation.

A subject could have multiple races; diabetes type was based on primary diagnosis; percentages (%) were calculated based on *n*.

n-values are only provided where they differed from the overall *N*-values.

'-' indicates term not present in relevant clinical study report.

• **CENTRAL SUBFIELD THICKNESS:** In both KESTREL and KITE, an initial rapid reduction in LS mean change from baseline in CSFT was observed in each treatment arm following the first treatment administration. Central subfield thickness continued to decrease up to Week 20, with effects maintained through Week 52 (Figures 3A, B). In general, no differences were observed between the brolucizumab and aflibercept arms at each post-baseline visit in KESTREL but greater reductions were consistently observed for the brolucizumab 6 mg arm in KITE, with the exception of Week 36. At Week 52 in KESTREL, the LS mean change from baseline in CSFT was –166 μm in the brolucizumab 6 mg arm compared with –160 μm in the aflibercept arm, with an estimated difference of –5 μm (95% CI: [–22, 12]). The estimated difference between the brolucizumab 3 mg arm and aflibercept arm was 4 μm (95% CI: [–15, 23]). At Week 52 in KITE, the LS mean estimate of change from baseline in CSFT was –197 μm in the brolucizumab 6 mg arm compared with –164 μm in the aflibercept arm, with an estimated difference of –33 μm (95% CI: [–53, –13]) favoring brolucizumab compared with aflibercept (Figures 3A, B).

For the average change from baseline in CSFT over the period Week 40 through Week 52, there were LS mean differences of +5 μm (95% CI: −12, 22) between the brolucizumab 3 mg arm and aflibercept arm, and −1 μm (95% CI: −18, 15) between the brolucizumab 6 mg arm and aflibercept arm in KESTREL. No superiority testing was performed due to the sequential multiple testing procedure. However, in KITE, the LS mean of the change from baseline in CSFT showed superior improvements in the brolucizumab 6 mg arm (–187 μm) compared with the aflibercept arm (–158 μm), with an estimated difference of –29 μm (95% CI: –49, –10; $P = .001$) favoring brolucizumab.

The proportions of subjects achieving CSFT <280 μm were consistently higher in the brolucizumab arms at the first predefined DA assessment at Week 32 and Week 52 (Figures 3C, D). At Week 32, the proportions of subjects with CSFT <280 μm in KESTREL were 43.7%, 47.1%, and 29.4% with brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept, respectively. The treatment difference between brolucizumab 3 mg and aflibercept was: 13.7% (95% CI: 5.1, 22.7); between brolucizumab 6 mg and aflibercept: 16.8% (95% CI: 8.3, 26.7). In KITE, the proportions of subjects with CSFT <280 μm at Week 32 were 48.0% vs 30.6% in brolucizumab 6 mg and aflibercept arms, respectively (treatment difference: 17.4% [95% CI: 7.7, 27.0]). At Week 52, the proportions of subjects with CSFT <280 μm in KESTREL were 48.4%, 54.0%, and 40.1% with brolucizumab 3 mg, brolucizumab 6 mg and aflibercept, respectively. The treatment difference between brolucizumab 3 mg and aflibercept was 7.8% (95% CI: –2.0, 17.6) and between brolucizumab 6 mg and aflibercept 13.4% (95% CI: 4.9, 23.7). In KITE, the proportions of subjects with CSFT <280 μm at Week 52 were 57.5% vs 41.4% in brolucizumab 6 mg and aflibercept arms, respectively (treatment difference: 16.3% [95% CI: 5.7, 25.9]).

• **SUBRETINAL FLUID AND/OR INTRARETINAL FLUID:** Compared with baseline, a lower proportion of subjects with retinal fluid was observed in all treatment arms at all post-baseline visits in both studies (Figures 4A, B). Lower proportions of subjects with retinal fluid were consistently observed for the brolucizumab 3 mg and 6 mg arms compared with the aflibercept arms from Week 40 through Week 52.

Looking specifically at Week 32 (the first DAA visit, 8 weeks after the fifth injection in the brolucizumab arms and the sixth injection in the aflibercept arm) and Week 52 (predefined secondary endpoint), a lower proportion of subjects in the brolucizumab arms had IRF and/or SRF compared with aflibercept in both KESTREL and KITE (Figures 4C, D). At Week 52, the proportions of subjects with IRF and/or SRF in KESTREL were 59.5%, 60.3%, and 73.3% in brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept arms, respectively. The treatment difference between brolucizumab 3 mg and aflibercept was −14.1% (95% CI: −23.3, −4.6), and −13.2% (95% CI: −23.2, −3.8) between brolucizumab 6 mg and aflibercept (Figure 4C).

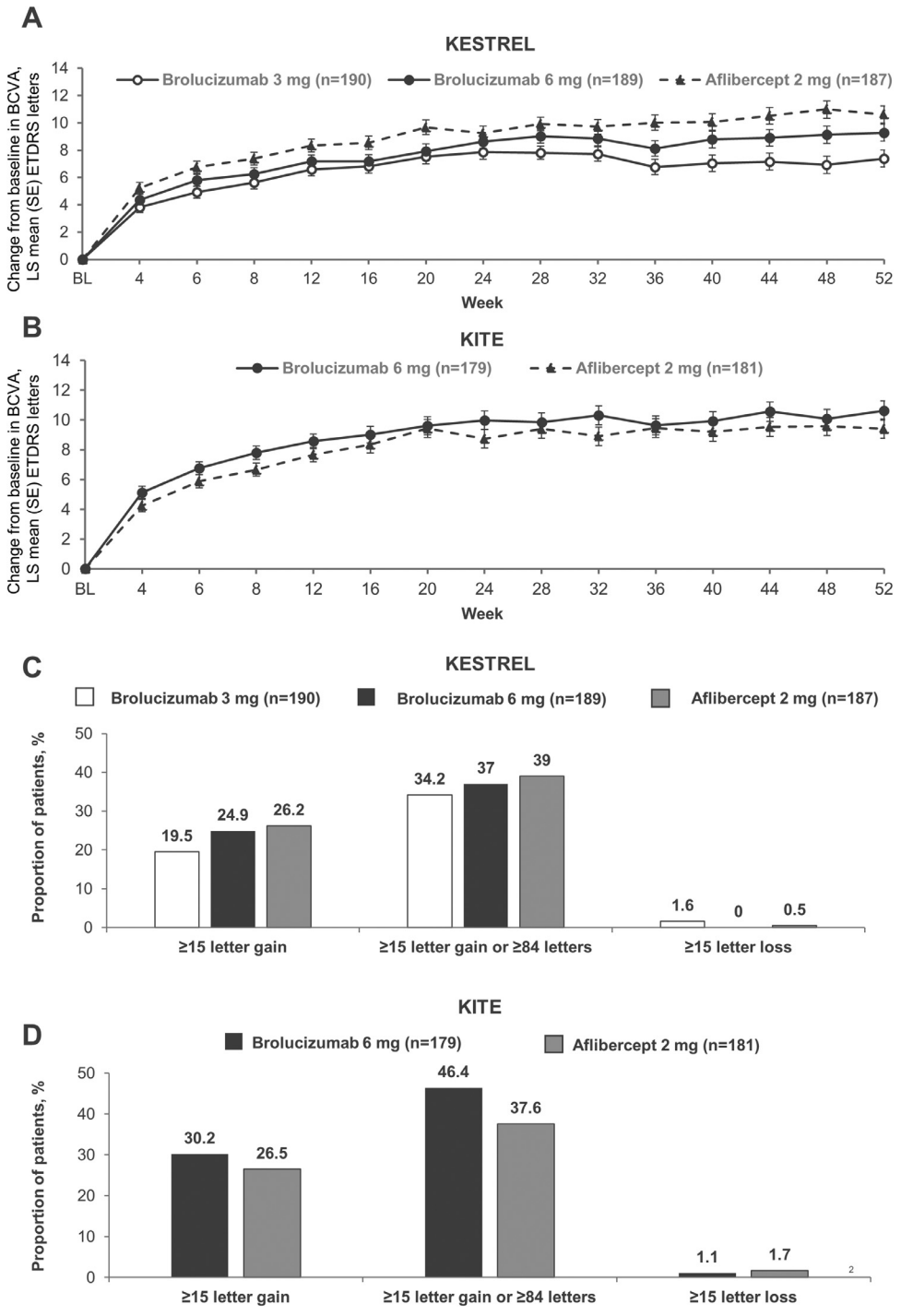

FIGURE 2. Mean change in BCVA from baseline to Week 52 in A) KESTREL and B) KITE. Proportion of subjects with 15-letter gain/loss in BCVA in C) KESTREL and D) KITE at Week 52. Full analysis set, last observation carried forward. BCVA = best corrected visual acuity, BL = baseline, ETDRS = Early Treatment Diabetic Retinopathy Study, LS = least squares, SE = standard error.

In KITE, the proportions of subjects with IRF and/or SRF at Week 52 were 54.2% in the brolucizumab 6 mg arm vs 72.9% in the aflibercept arm (treatment difference: −18.4% [95% CI: −28.5, −8.3]) (Figure 4D). These results are in line with those observed at Week 32.

• **Q12W DOSING MAINTENANCE OVER 52 WEEKS, Q8W TREATMENT NEED, AND NUMBER OF INJECTIONS TO WEEK 52:** For brolucizumab-treated eyes, the probabilities (Kaplan-Meier [K-M] estimates) for exclusively maintaining on q12w dosing after loading through Week 52 were

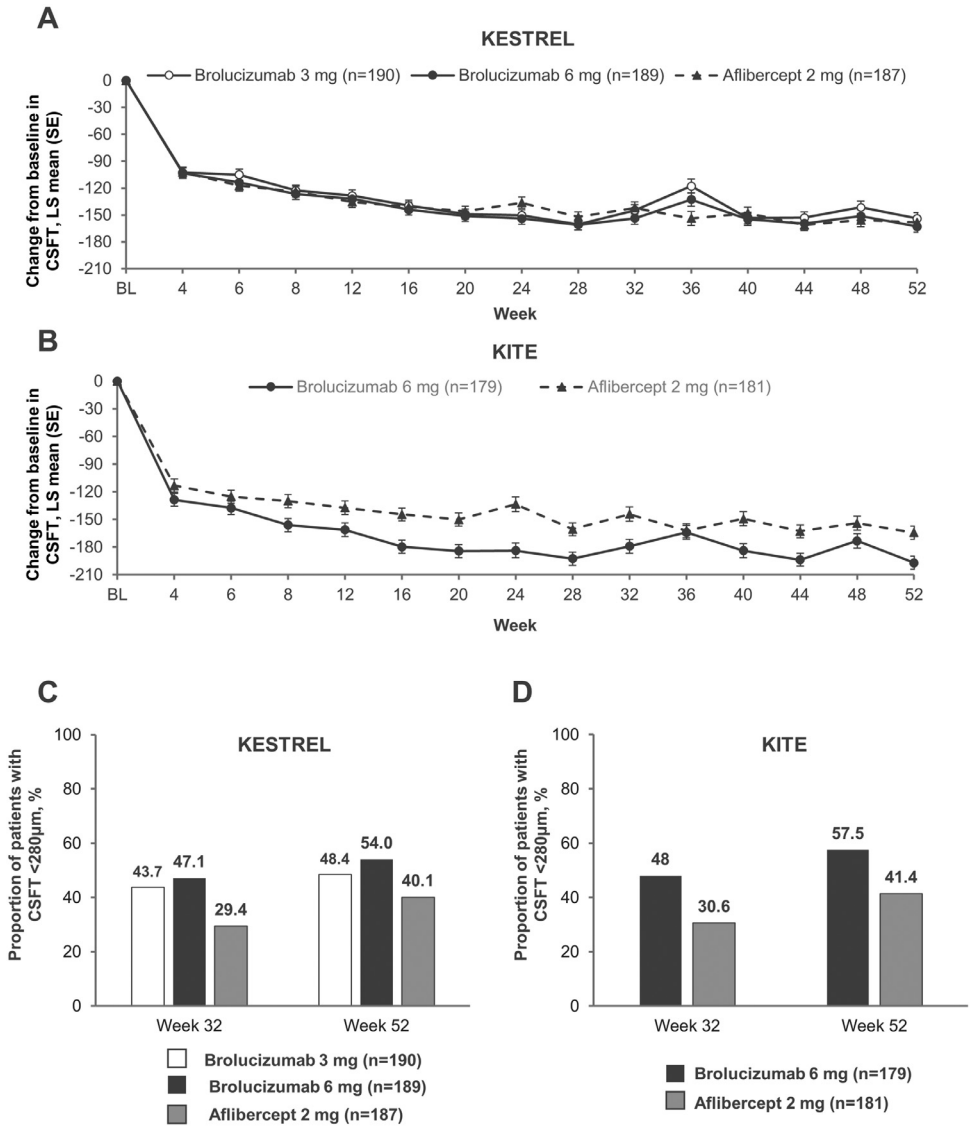

FIGURE 3. Mean change in central subfield thickness (CSFT) to Week 52 in A) KESTREL and B) KITE. Proportion of subjects achieving CSFT <280 µm with brolucizumab and aflibercept in C) KESTREL and D) KITE at Weeks 32 and 52. Full analysis set, last observation carried forward. CSFT = central subfield thickness, LS = least squares, SE = standard error.

47.4% for the 3 mg arm (95% CI for K-M estimate: [39.3, 55.1]) and 55.1% for the 6 mg arm (95% CI for K-M estimate: [46.9, 62.5]) in KESTREL and 50.3% for brolucizumab 6 mg (95% CI for K-M estimate: [42.5, 57.7]) in KITE (Table 2). Under the condition that a brolucizumab-treated eye successfully completed the first q12w interval with no observed disease activity, the probabilities for remaining on q12w dosing up to Week 52 increased to 87.0% for brolucizumab 3 mg (95% CI: [77.2, 92.8]) and 87.6% for brolucizumab 6 mg (95% CI: [78.8, 93.0]) in KESTREL and 95.1% for brolucizumab 6 mg (95% CI: [87.4, 98.1]) in KITE (Table 2).

At each DAA visit, a 'q8w treatment need' was recorded for any eye in which disease activity was identified by the masked investigator, regardless of the treatment arm. More subjects in the aflibercept arms had q8w treatment need at Week 32 (first DAA visit, 8 weeks after the last active injection in all treatment arms) compared with the brolucizumab arms in both KESTREL (brolucizumab 3 mg: 22.6%; brolucizumab 6 mg: 20.1%; aflibercept: 27.8%) and KITE (brolucizumab 6 mg: 24.2%; aflibercept: 39.8%) (Table 2).

Overall, during the loading and maintenance phases combined, the median number of active IVT injections up to Week 52 was 7 in all brolucizumab treatment arms and, due to the fixed q8w dosing schedule, 9 in the aflibercept arms (Table 2).

• **DIABETIC RETINOPATHY STATUS:** A clinically relevant improvement from baseline in the ETDRS DRSS score was observed in all treatment arms at Week 52. In KESTREL,

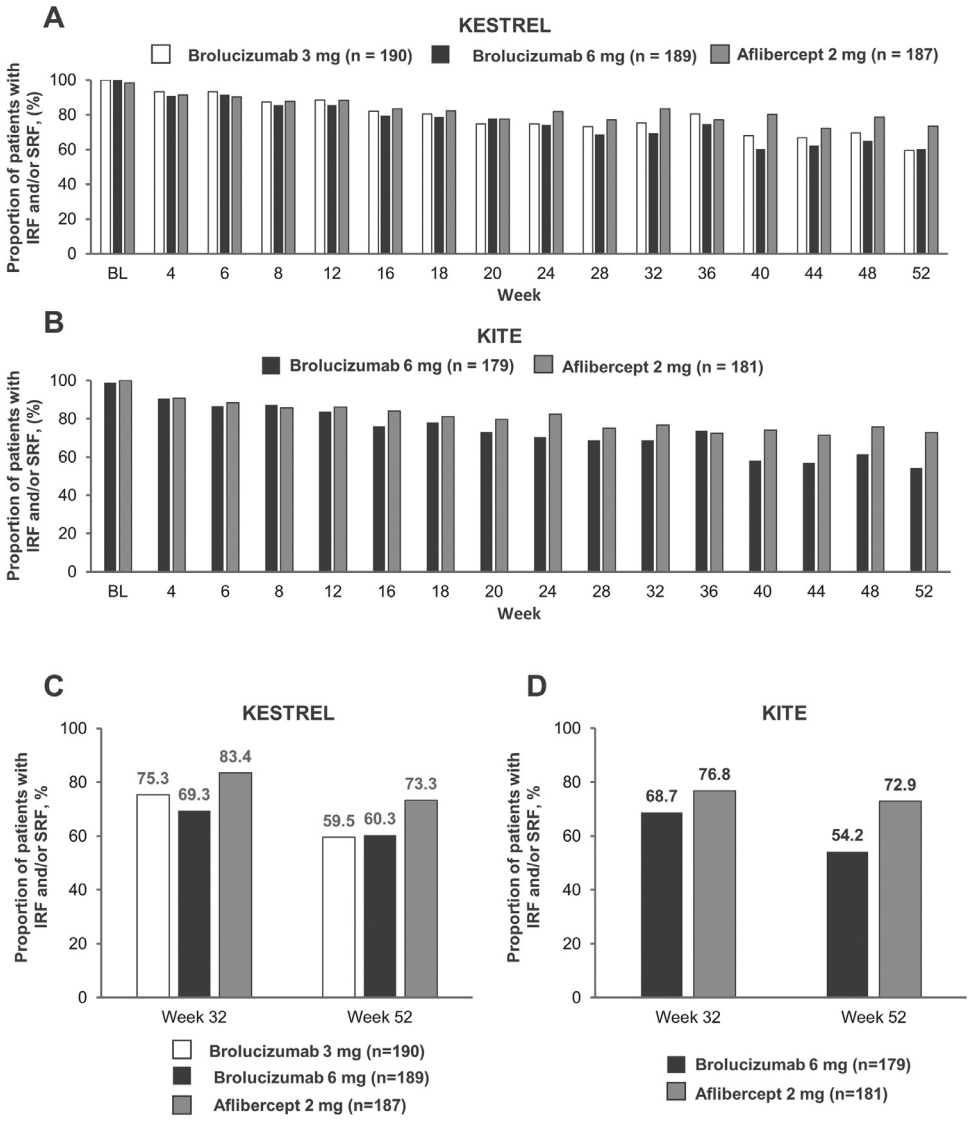

FIGURE 4. Proportion of patients with IRF and/or SRF present to Week 52 in A) KESTREL and B) KITE. Proportion of subjects with IRF and/or SRF at Weeks 32 and 52 in C) KESTREL and D) KITE. Full analysis set, last observation carried forward. IRF = intraretinal fluid, SRF = subretinal fluid.

the proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DRSS score at Week 52 was higher in the brolucizumab 3 mg arm (28.6%) and brolucizumab 6 mg arm (29.6%) compared with the aflibercept arm (21.7%). In the KITE study, the proportions were comparable between the 2 treatment arms (brolucizumab 6 mg, 29.0%; aflibercept, 27.7%; Supplementary Table 2). In a prespecified pooled KESTREL and KITE analysis, non-inferiority of brolucizumab 6 mg compared with aflibercept 2 mg with respect to the proportion of subjects with ≥ 2 step improvement in DRSS at Week 52 was established with a 10% non-inferiority margin (difference of 4% for brolucizumab 6 mg vs aflibercept; 95% CI: −0.6%, 8.6%; $P < .001$).

• **SAFETY:** Overall ocular and non-ocular adverse event rates were similar to those with aflibercept within each trial. A safety summary for both trials is shown in Table 3.

Ocular AEs were reported with comparable frequencies between the treatment arms in both studies up to Week 52. Overall, the most frequently reported ocular AEs by preferred term (PT) were conjunctival hemorrhage, cataract, and dry eye in both studies. Vitreous floaters, vitreous detachment, and diabetic retinal edema were most frequently reported in the KESTREL study. Eye pain and conjunctivitis were most frequently reported in the KITE study (Table 4).

Up to Week 52, non-ocular AEs were reported with comparable frequencies across treatment arms in the KESTREL

TABLE 2. Q12w Dosing Maintenance Over 52 Weeks, Q8w Treatment Status Need, and Number of Injections to Week 52

	KESTREL			KITE	
	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* = 187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
Subjects maintained on a q12w interval after loading to Week 52, %	47.4%	55.1%	N/A	50.3%	N/A
Subjects remaining on q12w at Week 52 within those who successfully completed the first q12w cycle at Week 36*, %	87.0%	87.6%	N/A	95.1%	N/A
Proportion of subjects with a q8w need at Week 32†, n/M (%)	35/155 (22.6)	32/159 (20.1)	45/162 (27.8)	40/165 (24.2)	66/166 (39.8)
Number of active injections up to Week 52					
Mean (SD)	6.8 (1.5)	6.8 (1.2)	8.5 (1.4)	7 (1.3)	8.5 (1.4)
Median	7	7	9	7	9
7 active injections, n (%)	96 (50.5)	106 (56.1)	5 (2.7)	93 (52.0)	5 (2.8)
8 active injections, n (%)	57 (30.0)	49 (25.9)	16 (8.6)	61 (34.1)	14 (7.7)
9 active injections, n (%)	–	–	149 (79.7)	–	145 (80.1)

*Censored: subjects were considered to no longer be under risk for a q8w-need identification at later visits. †A 'q8w need' was recorded for any eye in which disease activity was identified, regardless of the treatment regimen.

Efficacy/safety approach: censored data attributable to lack of efficacy and/or safety were imputed with q8w-need = Yes at the next DAA visit.

Abbreviations: q8w = every 8 weeks, q12w = every 12 weeks, SD = standard deviation.

Estimated percentages from Kaplan Meier analysis.

TABLE 3. Overall Safety Profile of Brolucizumab and Aflibercept in KESTREL and KITE

Adverse event	KESTREL			KITE	
	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* = 187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
Subjects with ≥ 1 AE, n (%)*					
Ocular (study eye)	81 (42.6)	76 (40.2)	73 (39.0)	53 (29.6)	52 (28.7)
Nonocular	122 (64.2)	128 (67.7)	122 (65.2)	108 (60.3)	127 (70.2)
Subjects with ≥ 1 serious AE, n (%)*					
Ocular (study eye)	7 (3.7)	2 (1.1)	4 (2.1)	4 (2.2)	3 (1.7)
Nonocular	23 (12.1)	35 (18.5)	37 (19.8)	30 (16.8)	37 (20.4)
Subjects with ≥ 15 letter loss from baseline at Week 52, %†	1.6%	0.0%	0.5%	1.1%	1.7%
Death, n (%)	1 (0.5)	5 (2.6)	2 (1.1)	3 (1.7)	2 (1.1)
AEs of special interest (study eye), *n* (%)					
Endophthalmitis‡	2 (1.1)	0	1 (0.5)	1 (0.6)	1 (0.6)
Intraocular inflammation§	9 (4.7)	7 (3.7)	1 (0.5)	3 (1.7)	3 (1.7)
- Retinal vasculitis§	3 (1.6)	1 (0.5)	0	0	0
Retinal vascular occlusion	2 (1.1)	1 (0.5)	0	1 (0.6)	1 (0.6)

Medical Dictionary for Regulatory Activities Version 23.0 (KITE) and 23.1 (KESTREL) used for the reporting of adverse events.

AE with a start date on or after the date of first study treatment administration were counted.

*A subject with multiple occurrences of an AE for a preferred term or system organ class was counted only once in each specific category.

‡Endophthalmitis cases in KITE: brolucizumab 6 mg, culture negative; aflibercept, culture positive. In KESTREL: brolucizumab 3 mg, one culture positive and one negative; aflibercept, culture positive.

§Percentages of subjects with intraocular inflammation and percentages of subjects with retinal vasculitis cannot be added up. Safety analysis set; † full analysis set-LOCF. Abbreviations: AE = adverse event, LOCF = last observation carried forward

TABLE 4. Ocular Adverse Events (≥2% in Any Treatment Arm) by Preferred Term For The Study Eye

Adverse event by preferred term	KESTREL			KITE	
	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* = 187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
Number of subjects with at least one AE	81 (42.6)	76 (40.2)	73 (39.0)	53 (29.6)	52 (28.7)
Conjunctival hemorrhage	17 (8.9)	14 (7.4)	18 (9.6)	7 (3.9)	6 (3.3)
Vitreous floaters	6 (3.2)	10 (5.3)	4 (2.1)	2 (1.1)	3 (1.7)
Cataract	6 (3.2)	9 (4.8)	8 (4.3)	4 (2.2)	6 (3.3)
Vitreous detachment	8 (4.2)	8 (4.2)	1 (0.5)	0	1 (0.6)
Intraocular pressure increased	5 (2.6)	6 (3.2)	0	1 (0.6)	3 (1.7)
Diabetic retinal edema	9 (4.7)	5 (2.6)	3 (1.6)	2 (1.1)	2 (1.1)
Dry eye	9 (4.7)	5 (2.6)	3 (1.6)	7 (3.9)	7 (3.9)
Eye irritation	3 (1.6)	5 (2.6)	3 (1.6)	1 (0.6)	1 (0.6)
Keratitis	0	4 (2.1)	3 (1.6)	-	-
Eye pain	4 (2.1)	3 (1.6)	3 (1.6)	6 (3.4)	3 (1.7)
Punctate keratitis	5 (2.6)	3 (1.6)	0	-	-
Visual acuity reduced	6 (3.2)	2 (1.1)	6 (3.2)	3 (1.7)	3 (1.7)
Retinal exudates	5 (2.6)	1 (0.5)	2 (1.1)	3 (1.7)	1 (0.6)
Vision blurred	5 (2.6)	1 (0.5)	1 (0.5)	1 (0.6)	3 (1.7)
Conjunctival hyperemia	4 (2.1)	0	1 (0.5)	-	-
Corneal abrasion	1 (0.5)	0	4 (2.1)	1 (0.6)	0
Iridocyclitis	4 (2.1)	0	0	3 (1.7)	0
Conjunctivitis	3 (1.6)	3 (1.6)	0	5 (2.8)	1 (0.6)
Eye pruritus	-	-	-	4 (2.2)	0

AEs with start date on or after the date of first study treatment administration were counted; AEs started after the subject discontinued study treatment and started alternative DME treatment in the study eye were censored; Preferred terms were sorted by descending frequency in the brolucizumab 6 mg arm. A subject with multiple occurrences of an AE for a preferred term was counted only once in each specific category.

MedDRA Version 23.1 was used for the reporting of AEs.

Safety analysis set; '-' indicates term not present in relevant clinical study report.

study (64.2% in the brolucizumab 3 mg arm, 67.7% in the brolucizumab 6 mg arm, and 65.2% in the aflibercept arm), whereas the incidence was lower in the brolucizumab 6 mg arm (60.3%) compared with the aflibercept arm (70.2%) in the KITE study (Supplementary Table 3).

Ocular SAEs were reported in 3.7% of subjects in the brolucizumab 3 mg arm, 1.1% of subjects in the brolucizumab 6 mg arm, and 2.1% of subjects in the aflibercept arm for the KESTREL study. In KITE, ocular SAEs were reported in 2.2% of subjects in the brolucizumab 6 mg arm and in 1.7% of subjects in the aflibercept arm (Table 5). The incidence of non-ocular SAEs was lower in the brolucizumab 3 mg arm (12.1%) compared with the brolucizumab 6 mg arm (18.5%) and the aflibercept arm (19.8%) in the KESTREL study. In KITE, the incidence of non-ocular SAEs was numerically lower in the brolucizumab 6 mg arm compared with the aflibercept arm (16.8% vs 20.4%, respectively). There were 8 deaths in the KESTREL study (1 [0.5%] in the brolucizumab 3 mg arm, 5 [2.6%] in the brolucizumab 6 mg arm, and 2 [1.1%] in the aflibercept arm), whereas there were 5 deaths in KITE (3 [1.7%] in the brolucizumab arm and 2 [1.1%] in the aflibercept arm). The investigator suspected none of the deaths to be related to study treatment (Supplementary Table 4).

In KESTREL and KITE, intraocular inflammation (including retinal vasculitis), retinal vascular occlusion, and endophthalmitis were considered to be adverse events of special interest (Table 3). Intraocular inflammation (IOI) was reported in KESTREL in 4.7% ($n = 9$), 3.7% ($n = 7$), and 0.5% ($n = 1$) of subjects in the brolucizumab 3 mg and 6 mg, and aflibercept arms, respectively. In KITE, IOI was reported in a similar proportion of subjects in the brolucizumab 6 mg (1.7% [$n = 3$]) and aflibercept arms (1.7% [$n = 3$]). Taking both studies together, there was a total of 17 events in the brolucizumab 3 mg group (in 9 subjects: 6 male/3 female), 13 events in the brolucizumab 6 mg group (in 10 subjects: 4 male/6 female), and 5 events in the aflibercept group (in 4 subjects: 1 male/3 female). Most events of intraocular inflammation were mild or moderate in severity (10/13 in the brolucizumab 6 mg group, 5/5 in the aflibercept group, and 13/17 in the brolucizumab 3 mg group) and resolved with routine clinical care without sequelae.

TABLE 5. Ocular Serious Adverse Events by Primary System Organ Class and Preferred Term For The Study Eye

Primary system organ class and preferred term *n* (%)	KESTREL			KITE	
	Brolucizumab 3 mg *N* = 190	Brolucizumab 6 mg *N* = 189	Aflibercept 2 mg *N* = 187	Brolucizumab 6 mg *N* = 179	Aflibercept 2 mg *N* = 181
Number of subjects with at least one AE	7 (3.7)	2 (1.1)	4 (2.1)	4 (2.2)	3 (1.7)
Eye disorders	6 (3.2)	2 (1.1)	4 (2.1)	2 (1.1)	2 (1.1)
Conjunctival cyst	0	1 (0.5)	0	-	-
Diabetic retinal edema	0	1 (0.5)	0	-	-
Pterygium	0	1 (0.5)	0	-	-
Vitreous floaters	0	1 (0.5)	0	-	-
Cataract	0	0	3 (1.6)	-	-
Glaucoma	1 (0.5)	0	0	1 (0.6)	0
Macular fibrosis	1 (0.5)	0	0	-	-
Macular edema	1 (0.5)	0	0	-	-
Ophthalmic herpes zoster	-	-	-	1 (0.6)	0
Optic nerve disorder	1 (0.5)	0	0	-	-
Retinal artery occlusion	-	-	-	1 (0.6)	0
Retinal detachment	1 (0.5)	0	1 (0.5)	0	1 (0.6)
Retinal tear	-	-	-	0	1 (0.6)
Retinal vasculitis	3 (1.6)	0	0	-	-
Retinal vein thrombosis	1 (0.5)	0	0	-	-
Uveitis	1 (0.5)	0	0	1 (0.6)	1 (0.6)
Vitritis	1 (0.5)	0	0	-	-
Infections and infestations	2 (1.1)	0	1 (0.5)	2 (1.1)	1 (0.6)
Endophthalmitis	2 (1.1)	0	1 (0.5)	1 (0.6)	1 (0.6)

AEs with start date on or after the date of first study treatment administration were counted. AEs started after the subject discontinued study treatment and started alternative DME treatment in the study eye were censored.

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by descending frequency in the brolucizumab 6 mg arm. A subject with multiple occurrences of an AE for a preferred term or system organ class was counted only once in each specific category.

MedDRA Version 23 1 was used for reporting of adverse events.

Safety analysis set; '-' indicates term not present in relevant clinical study report.

Abbreviations: AE = adverse event, AEs = adverse events, *n* = number of subjects, *N* = total number of subjects, PT = preferred term.

Retinal vasculitis was reported in KESTREL in 1 (0.5%) subject in the brolucizumab 6 mg arm (Table 3) and this same subject also experienced retinal artery occlusion (RAO). The day of onset of retinal vasculitis was Day 114 (i.e. 114 days from baseline) and the event was classed as mild, whereas the RAO began on Day 136 (22 days after the onset of ongoing retinal vasculitis) and was moderate in severity; both events resolved without any treatment and the subject exhibited a 14-letter BCVA gain at Week 52 compared with baseline (BCVA at baseline, 72 letters). In the brolucizumab 3 mg arm, 3 (1.6%) subjects reported retinal vasculitis: 1 began on Day 115 and was classed as mild, 1 began on Day 96 and was classed as severe, and the other began on Day 203 and was also classed as severe. This last subject also experienced concurrent RAO that was still ongoing at Week 52. At the time of end of the vasculitis events, all 3 subjects either gained vision or had ≤ 5 letter loss compared with baseline; the ongoing RAO subject had gained 2 letters compared with baseline at Week 52. One subject in the brolucizumab 3 mg arm reported retinal vein thrombosis without vasculitis on Day 291; this subject had 3 episodes of iridocyclitis and neovascular glaucoma prior to retinal vein thrombosis and lost 39 letters from baseline at Week 52. No cases of retinal vasculitis were reported in the aflibercept arm in KESTREL or in either of the treatment arms in KITE. There were 2 cases of RAO reported in KITE (1 case each in the brolucizumab 6 mg and aflibercept arms) without IOI prior to the events. The aflibercept subject did not lose vision (+12 letters at Week 52 compared with baseline) but the brolucizumab 6 mg subject had severe vision loss (–75 letters compared with baseline). As this subject had an ongoing retinal vascular disorder (from prior to study entry) and was suffering from a head injury with scalp bleeding due to a recent fall, the investigator judged the event of retinal arterial occlusion as not suspected to be related to study treatment or injection procedure.

Endophthalmitis was reported in KESTREL in 2 (1.1%) subjects in the brolucizumab 3 mg arm and in 1 (0.5%) sub-

ject in the aflibercept arm (Table 3). There were no endophthalmitis cases reported in the brolucizumab 6 mg arm. In KITE, endophthalmitis was reported in 1 (0.6%) subject in the brolucizumab 6 mg arm and in 1 (0.6%) subject in the aflibercept arm. Three out of the total 5 endophthalmitis cases in both studies were culture-positive (1 event with brolucizumab 3 mg and 2 events with aflibercept). The remaining 2 events were culture-negative: 1 in brolucizumab 3 mg in KESTREL, who lost 61 letters from baseline at the end of the AE, and 1 in brolucizumab 6 mg in KITE, who gained 27 letters from baseline at the end of the AE.

A small number of subjects lost ≥ 15 letters at Week 52 when compared with baseline in both studies. In KESTREL, there were 3 (1.6%) subjects in the brolucizumab 3 mg arm (1 with 2 events of iridocyclitis, 1 event of vitritis, and 22 letters lost; 1 subject with endophthalmitis as described above and 74 letters lost, and 1 subject as described above with retinal vein thrombosis and 39 letters lost), 1 (0.5%) subject in the aflibercept arm (who lost 29 letters from baseline at the early exit visit following an event of endophthalmitis) and no subjects lost ≥ 15 letters at Week 52 when compared with baseline in the brolucizumab 6 mg arm. In KITE, there were 2 (1.1%) subjects in the brolucizumab 6 mg arm (1 with iridocyclitis and uveitis and 16 letters lost, and 1 subject with RAO, as described above, and 75 letters lost) and 3 (1.7%) in the aflibercept arm (2 subjects with cataract lost 17 letters and 25 letters, respectively, and 1 subject with retinal detachment and retinal tear lost 18 letters from baseline at Week 52).

• **IMPACT OF THE COVID-19 PANDEMIC:** There was an increase in the number of protocol deviations such as missing study visits or subject discontinuations in each treatment arm due to the COVID-19 pandemic. Nevertheless, in terms of efficacy, there were no differences observed between the treatment effects when the primary and secondary endpoints presented here were analyzed by subgroup of COVID-19 exposure and impact. The results in the COVID-19 exposed/non-exposed and impacted/non-impacted subgroups remained consistent with those from the overall population.

DISCUSSION

KESTREL and KITE met the primary endpoint of non-inferiority in BCVA change from baseline at Week 52 of brolucizumab 6 mg vs aflibercept, with >50% of brolucizumab 6 mg subjects being maintained on a q12w interval through Week 52. In KESTREL, the LS mean estimate for the BCVA change from baseline at Week 52 was +9.2 letters in the brolucizumab 6 mg arm compared with +10.5 letters in the aflibercept arm; in KITE, the LS mean estimate was +10.6 letters in the brolucizumab 6 mg arm compared with +9.4 letters in the aflibercept arm. Moreover, anatomical outcomes, as determined by CSFT reduction and retinal fluid resolution, favored brolucizumab 6 mg over aflibercept. The incidence of ocular SAEs and AEs of special interest associated with brolucizumab 6 mg were low in both studies, although the overall risk of IOI, retinal vasculitis, and retinal vascular occlusion were higher in brolucizumab-treated eyes compared with aflibercept-treated eyes. The primary 52-week outcomes reported here are validated by the pivotal VIVID and VISTA trials with aflibercept.[8] The observed gains in BCVA of +10.5 and +9.4 letters in the aflibercept 2 mg arm in KESTREL and KITE, respectively, are consistent with the outcomes of the VIVID and VISTA studies (+10.5 to +12.5 letters gain across the different arms, with a lower mean BCVA at baseline ranging from 58.8 to 60.8 letters as compared with a baseline range of 65.2 to 66.6 letters in KESTREL and KITE).[8]

Focusing on anatomical outcomes, lower proportions of subjects with retinal fluid were observed for brolucizumab compared with aflibercept at Week 32 and Week 52 in both studies. At Week 52, 13% to 18% fewer subjects had SRF and/or IRF in the brolucizumab 6 mg arm, which was achieved with a median of 7 injections compared with 9 in the aflibercept arms. Already at Week 32, 8 weeks after an active injection in all treatment arms, a reduction in the proportion of subjects with SRF and/or IRF in the brolucizumab arm was apparent, with 1 less injection. From the RISE and RIDE studies, it is evident that early treatment of macular edema is important in DME to prevent avoidable vision loss.[6,7] Also, in a post hoc analysis of the Protocol I study, persistent macular edema resulted in lower visual gains in subjects with DME, as eyes with the longest DME duration and highest amount of excess edema (CRT ≥250 μm) gained a mean 9.3 fewer BCVA letters over the 3-year period than eyes with the least amount of edema.[21] Furthermore, eyes with the highest cumulative number of visits with persistent edema (CRT ≥250 μm) gained 4 to 6 fewer ETDRS letters over the 3-year period than eyes with the least number of visits with persistent edema.[21] With its better fluid resolution, brolucizumab should therefore help to achieve 1 of the main aims of anti-VEGF therapy, which is to reliably resolve retinal fluid as early and as far as possible for optimal visual outcomes in patients with DME.

Anti-VEGFs in DME are typically administered monthly until the macula is dry, and thereafter administrated using either PRN or a treat-and-extend regimen.[22] However, the number of injection and monitoring visits required in clinical trial settings investigating these treatment regimens is often unsustainable for many patients in the real world.[23-26] The resulting low levels of adherence and compliance have been shown to have a negative impact on visual acuity gains.[15,27,28] Therefore, a goal of DME management is to determine therapeutic needs on an individual basis and treat accordingly to achieve an optimal visual outcome with minimal numbers of clinic visits and intravitreal injection burden. In KESTREL and KITE, 55.1% and 50.3% of brolu-

cizumab 6 mg subjects were maintained on a q12w interval immediately after the 6-weekly loading to Week 52. Moreover, the dosing interval through the first 12-week treatment interval was highly predictive of the subsequent dosing interval: 87.0% of subjects in the brolucizumab 3 mg and 87.6% in the brolucizumab 6 mg arms in KESTREL and 95.1% of brolucizumab 6 mg subjects in KITE with no q8w need during the initial q12w cycle remained on a q12w interval at Week 52. In clinical practice, these robust predictability results should help physicians to confidently determine the patients who are suitable for brolucizumab q12w dosing soon after the loading phase, thus providing an efficient treatment scheduling approach.

In the nAMD indication, post-marketing cases of retinal vasculitis and retinal occlusive vasculitis have been detected in relation to the use of brolucizumab and, although not originally reported by the investigators, these adverse events were subsequently identified in an unmasked, post hoc review of the pooled brolucizumab arms from HAWK and HARRIER.[29] This post hoc review concluded that 4.6% of brolucizumab subjects in HAWK and HARRIER had definite or probable IOI, 3.3% of whom also may fall into the spectrum of retinal vasculitis, and 2.1% of these also into the spectrum of retinal vascular occlusion (RO). Here in subjects with DME, safety measures were immediately put in place to alert KESTREL and KITE investigators to the new safety signal, and trial protocols were amended to stipulate that an IVT injection was not to be performed if any signs of inflammation were identified. Trial subjects were also instructed to report any abnormal symptoms or signs without delay and investigational sites had to make every effort to bring the subject for immediate examination and timely initiation of treatment according to clinical care. The reported rates of IOI in DME studies were similar to HAWK and HARRIER in KESTREL, but the incidence of retinal vasculitis was lower (3 subjects (1.6%) in the brolucizumab 3 mg arm [1 of whom also developed RAO] and 1 subject (0.5%) in the brolucizumab 6 mg arm, who also had an RAO event). In KITE, rates of IOI were much lower with 3 subjects (1.7%) in both the brolucizumab 6 mg and aflibercept arms, none of whom developed concurrent retinal vasculitis or retinal vascular occlusions. Potential explanations for the lower number of IOI-related adverse events compared with HAWK and HARRIER include differences between the underlying diseases of nAMD and DME, differences between the studies, or the less intensive q6w loading phase in KESTREL and KITE. Nevertheless, there was inter-study variability between KESTREL and KITE and the sample sizes of these Phase III studies were powered for primary efficacy rather than safety endpoints. It is therefore crucial to highlight that post-marketing adverse events will be closely monitored and analyzed once brolucizumab is approved and launched for DME patients. Overall, the 52-week data did not show any new safety concerns, despite diabetes being a vascular and pro-inflammatory disease.

The results observed for brolucizumab 6 mg in KESTREL and KITE (i.e. a comparable effect on BCVA as aflibercept, with a lower number of injections after the loading phase and improvement in retinal fluid) are consistent with the outcome of HAWK and HARRIER, the pivotal studies with brolucizumab in patients with nAMD.[18,19] Although the studies are in 2 distinct indications, the overall advantages in anatomical parameters with fewer injections support the underlying hypothesis that a lower molecular weight anti-VEGF combined with a higher concentration gradient between vitreous and retina increase the drug distribution to the target site, resulting in improved control of anatomical disease activity.[17]

The main strengths of the KESTREL and KITE studies are that they are 2 large, double-blinded Phase III trials that are the first to compare brolucizumab with aflibercept for the treatment of visual impairment due to DME. The q6w loading phase for brolucizumab is also the first time this initial injection frequency has been compared with q4w for other anti-VEGFs in DME. An additional strength is the use of independent, masked image reading center graders with experience in DME studies for grading all images. For limitations, there is no head-to-head comparison with aflibercept and the treatment regimens did not allow brolucizumab groups to be extended from q8w to q12w once they were adjusted to q8w, and the aflibercept group was fixed q8w dosing in the maintenance phase. Diabetic macula edema tends to be a chronic disease often requiring long-term treatment. The 100-week results will provide additional insight into the safety and efficacy of q12w/q8w brolucizumab vs that of q8w aflibercept.

In summary, the brolucizumab 52-week results in the KESTREL and KITE studies demonstrate clinically meaningful visual acuity gains and excellent anatomic improvements with an overall favorable benefit/risk profile; therefore, brolucizumab could provide an additional therapeutic option in DME that reduces the burden on patients, physicians, and the health care system.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

David M. Brown: Investigation, Writing – review & editing. **Andrés Emanuelli:** Investigation, Writing – review & editing. **Francesco Bandello:** Investigation, Writing – review & editing. **Jose Juan Escobar Barranco:** Investigation, Writing – review & editing. **João Figueira:** Investigation, Writing – review & editing. **Eric Souied:** Investigation, Writing – review & editing. **Sebastian Wolf:** Investigation, Writing – review & editing. **Vishali Gupta:** Investigation, Writing – review & editing. **Nor Fariza Ngah:** Investigation, Writing – review & editing. **Gerald Liew:** Investigation, Writing – review & editing. **Raman Tuli:** Investigation, Writing – review & editing. **Ramin Tadayoni:** Investigation, Writing – review & editing. **Dilsher Dhoot:** Investigation, Writing – review & editing. **Lixin Wang:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Emmanuel Bouillaud:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Ying Wang:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Lidija Kovacic:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Nicolas Guerard:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Justus G. Garweg:** Investigation, Writing – review & editing.

Funding/Support: Financial support was provided by Novartis (Basel, Switzerland). The sponsor or funding organization participated in the design of the study; management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript**. Financial disclosures: D.B.** Consultant for Novartis, Roche and Bayer**; A.E.** Research funding from Novartis, Regeneron, Roche, and Adverum Biotechnologies**; F.B.** Allergan, Bayer, Boehringer-Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss**; J.J.E.B.** Consultant for Novartis, Bayer, Roche; Speaker for Novartis, Allergan, Bayer; Research funding from Novartis, Allergan, Roche, Kodiak Sciences Inc., SamChunDang Pharm. Co. Ltd., IVERIC BIO, Inc., Boehringer Ingelheim; **J.F.** Consultant for Allergan, Bayer, Boehringer, Novartis, Roche; Speaker for Alcon, Alimera Sciences; **E.S.** Financial support from Allergan, Bayer, Novartis, Roche, Thea**; S.W.** Consultant for Bayer, Boehringer-Ingelheim, Chengdu Kanghong Biotech, Zeiss, and Roche; grant support from Zeiss and Heidelberg Engineering**; V.G.** Nothing to disclose**; N.F.N.** Advisor for Novartis, Allergan**; G.L.** Consultant for Novartis, Bayer**; R.T.** Consultant for Roche; Research grants Roche, Novartis, Appelis**; R.T.** Advisor: Alcon, Allergan, Bayer, Genentech, Novartis, Oculis, Roche, Thea, Zeiss**; D.D.** Consultant/Advisor for Alimera Sciences, Allergan, Bayer Healthcare Pharmaceuticals, EyePoint Pharmaceuticals, Genentech, Novartis, Alcon Pharmaceuticals, Optos, Inc., Regeneron, Santen, Inc**; L.W., E.B., Y.W, L.K., N.G.** Employees of Novartis**; J.G.** Consultant for Bayer, Novartis, Chengdu Kanghong, Allergan; has participated in industry-sponsored studies from Novartis, Bayer, Chengdu Kanghong, AbbVie, Alcon.

Author contributions: L.W., E.B., Y.W, L.K., N.G. were involved in the conception and design of the study and D.B., A.E., F.B., J.J.E.B., J.F., E.S., S.W., N.F.N., G.L., R.T., R.T., D.D., J.G. were involved in data collection. All authors made substantial contributions to the analysis and interpretation of data, drafting the article and revising it critically, and final approval of the version to be submitted. Medical writing support was provided by Susan Simpson, PhD (Novartis Ireland Ltd.) and Indumathy Pinnamaneni (Novartis Healthcare Pvt. Ltd., Hyderabad, India), in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The funding for this writing support was provided by Novartis. All authors attest that they meet the current ICMJE criteria for authorship.

Data presented at: The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting (Virtual), 1–7 May 2021 and EURETINA Virtual 2021, 9—12 September 2021.

REFERENCES

1. Teo ZL, Tham Y-C, Yan Yu MC, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: Systematic review and meta-analysis. *Ophthalmology*. 2021. doi:10.1016/j.ophtha.2021.04.027.
2. Thomas RL, Halim S, Gurudas S, et al. IDF Diabetes Atlas: A review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. *Diabetes Res Clin Pract*. 2019;157:107840.
3. Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, et al. Diabetic macular edema pathophysiology: Vasogenic versus inflammatory. *J Diabetes Res*. 2016;2016:2156273.
4. Daruich A, Natet A, Moulin A, et al. Mechanisms of macular edema: Beyond the surface. *Prog Retin Eye Res*. 2018;63:20–68.
5. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615–625.
6. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789–801.
7. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10):2013–2022.
8. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121(11):2247–2254.
9. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122(10):2044–2052.
10. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2017;237:185–222.
11. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123:1351–1359.
12. Bressler SB, Ayala AR, Bressler NM, et al. Persistent macular thickening after ranibizumab treatment for diabetic macular edema with vision impairment. *JAMA Ophthalmol*. 2016;134(3):27 8-285.

13. Blinder KJ, Dugel PU, Chen S, et al. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). *Clin Ophthalmol*. 2017;11:393–401.
14. Long AN, Dagogo-Jack S. The comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. *J Clin Hypertens (Greenwich)*. 2011;13(4):244–251.
15. Weiss M, Sim DA, Herold T, et al. Compliance and adherence of patients with diabetic macular edema to intravitreal anti-vascular endothelial growth factor therapy in daily practice. *Retina*. 2018;38(12):2293–2300.
16. Jansen ME, Krambeer CJ, Kermany DS, et al. Appointment compliance in patients with diabetic macular edema and exudative macular degeneration. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49:186–190.
17. Nguyen QD, Das A, Do DV, et al. Brolucizumab: Evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration. *Ophthalmology*. 2020 Jan 17:S0161-6420(20)30041-5. doi:10.1016/j.ophtha.2019.12.031.
18. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72–84.
19. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: Ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128:89–99.
20. EYLEA (aflibercept) Injection [package insert]. Tarrytown, NY: Regeneron pharmaceuticals, inc.; July 2014. http://www.regeneron.com/Eylea/eylea-fpi.pdf
21. Sadda SR, Campbell J, Dugel PU, et al. Relationship between duration and extent of oedema and visual acuity outcome with ranibizumab in diabetic macular oedema: A post hoc analysis of Protocol I data. *Eye (Lond)*. 2020;34(3):480–490.
22. Kaya M, Kocak N, Ozturk T, et al. Intravitreal ranibizumab and dexamethasone implant injections as primary treatment of diabetic macular edema: simultaneously double protocol. *Eye (Lond)*. 2021;35(3):777–785.
23. Mitchell P, Sheidow TG, Farah ME, et al. Effectiveness and safety of ranibizumab 0.5 mg in treatment-naïve patients with diabetic macular edema: Results from the real-world global LUMINOUS study. *PLoS One*. 2020;15(6):e0233595.
24. Menchini U, Bandello F, De Angelis V, et al. Ranibizumab for visual impairment due to diabetic macular edema: real-world evidence in the Italian population (PRIDE Study). *J Ophthalmol*. 2015;2015:324841.
25. Ziemssen F, Wachtlin J, Kuehlewein L, et al. Intravitreal ranibizumab therapy for diabetic macular edema in routine practice: Two-year real-life data from a non-interventional, multicenter study in Germany. *Diabetes Ther*. 2018;9(6):2271–2289.
26. Stefanickova J, Cunha-Vaz J, Ulbig M, et al. A noninterventional study to monitor patients with diabetic macular oedema starting treatment with ranibizumab (POLARIS). *Acta Ophthalmol*. 2018;96(8):e942–e949.
27. Ramakrishnan MS, Yu Y, Vanderbeek BI. Visit adherence and visual acuity outcomes in patients with diabetic macular edema: A secondary analysis of DRCRnet Protocol T. *Clin Exp Ophthalmol*. 2021;259:1419–1425.
28. Angermann R, Hofer M, Huber AL, et al. The impact of compliance among patients with diabetic macular oedema treated with intravitreal aflibercept: A 48-month follow-up study. *Acta Ophthalmol*. 2021 Jun 17. doi:10.1111/aos.14946.
29. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis and retinal occlusion-related events with brolucizumab: post-hoc review of HAWK and HARRIER. *Ophthalmology*. 2020 S0161-6420(20)31075-7.