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KESTREL and KITE Phase 3 studies: 100-week results with brolucizumab in patients with diabetic macular edema

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Running head: Brolucizumab for the treatment of diabetic macular edema

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; CSFT, central subfield thickness; DAA, Disease Activity Assessment; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; IOI, intraocular inflammation; IRF, intraretinal fluid; LS means, least squares means; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; q6w, every 6 weeks; q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks; SAE, serious AE; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

Key words: Aflibercept; brolucizumab; diabetic macular edema; q12w, q16w

Supplemental material is available at AJO.com.

ABSTRACT

Purpose: To report the 100-week outcomes from KESTREL and KITE.

Design: Two phase 3, double-masked, active-controlled, randomized trials.

Methods: Patients with diabetic macular edema (DME) were randomized 1:1:1 to brolucizumab 3 mg/6 mg (BRO3/BRO6) or aflibercept 2 mg (AFL) in KESTREL (N=566) or 1:1 to BRO6 or AFL in KITE (N=360). BRO3/BRO6 arms received 5 loading doses every 6 weeks (q6w) followed by q12w dosing, with an option to adjust to q8w at predefined disease activity assessment visits. In KITE, at Week 72, based on the disease stability assessment, treatment

intervals could be extended by 4 weeks in the BRO6 arm. AFL arms received 5 monthly loading doses followed by fixed q8w dosing.

Results: At Week 100, change from baseline in BCVA (letters) was +8.8 for BRO6 and +10.6 for AFL in KESTREL; +10.9 for BRO6 and +8.4 for AFL in KITE. In both studies, fewer BRO6 subjects had intraretinal fluid and/or subretinal fluid versus (vs) AFL. Results were achieved with 32.9% (KESTREL) and 47.5% (KITE) of BRO6 subjects maintained on q12w and q12w/q16w dosing, respectively. Intraocular inflammation rates for BRO6 vs AFL were 4.2% vs 1.1% (KESTREL) and 2.2% vs 1.7% (KITE) of which retinal vasculitis rates were 0.5% vs 0% in KESTREL, with no cases in KITE. Retinal vascular occlusion rates were 1.6% vs 0.5% (KESTREL) and 0.6% in both treatment arms in KITE.

Conclusion: Results show the long-term efficacy and durability of brolucizumab in improving visual and anatomical outcomes in DME; the overall safety profile of brolucizumab remained unchanged through Year 2.

INTRODUCTION

Diabetic macular edema (DME) is a sight-threatening complication in patients with diabetes, associated with microvascular damage and leakage of fluid, proteins, and lipids in the macula, which can lead to visual impairment and blindness. The prevalence of DME is projected to continue to rise in the coming decades, globally.[1] Despite advances in treatment options, there continues to be a significant unmet need for effective and safe therapies with extended durability.

Although intravitreal anti-vascular endothelial growth factors (anti-VEGFs), the first-line treatment in DME, have proven efficacy in improving visual acuity (VA) and anatomical outcomes, suboptimal VA gains are common in routine clinical practice, an observation at least partially attributable to undertreatment.[2-4] VA gains have consistently been demonstrated to

correlate with anti-VEGF dosing frequency.[5] Even with flexible dosing regimens such as *pro re nata* and treat and extend, a considerable burden of treatment and monitoring visits remains.[6, 7] This, combined with the complex comorbidity profile of patients with DME, may contribute to clinical non-adherence, resulting in undertreatment and overall suboptimal VA outcomes.[8, 9] Consistent with this, 25% to 30% of patients with DME have been reported to be lost to follow-up within just 1 year.[10, 11]

Brolucizumab is a single-chain antibody fragment with high affinity for VEGF-A. Its low molecular weight (26kDa) enables the delivery of a high anti-VEGF-molar binding capacity per injection compared with other anti-VEGFs and offers the potential for more effective tissue penetration and increased duration of action.[12] Brolucizumab is approved for the treatment of neovascular age-related macular degeneration (nAMD) across more than 70 countries based on the Phase 3 HAWK and HARRIER studies, in which brolucizumab 6 mg showed comparable vision gains with superior anatomical outcomes and better fluid resolution than aflibercept, with >50% of subjects maintained on a every 12-week dosing (q12w) after loading up to Week 48.[13] However, following reports of retinal vasculitis (RV), including retinal occlusive vasculitis in patients with nAMD,[14] a safety signal of RV and/or retinal vascular occlusion (RO) that may result in severe vision loss was raised with brolucizumab; typically, these events occur in the presence of intraocular inflammation (IOI).[15]

KESTREL and KITE were two pivotal, 100-Week, Phase 3 studies evaluating the efficacy and safety of brolucizumab in patients with visual impairment due to DME. The primary results from these trials demonstrated that brolucizumab 6 mg was non-inferior to aflibercept 2 mg in VA gains from baseline at Week 52, with greater fluid resolution. These outcomes were achieved with >50% patients maintained on a q12w dosing interval, immediately after 5 loading doses every 6 weeks (q6w), up to Week 52.[16]

Based on these data, brolucizumab has received approval in more than 40 countries worldwide for the treatment of visual impairment due to DME, including in the European Union in March 2022 and by the US Food and Drug Administration in May 2022.[17, 18] The aim of the current report is to present the 2-year (100-week) results from the KESTREL and KITE studies.

METHODS

KESTREL (NCT03481634; conducted between July 2018 and October 2021) and KITE (NCT03481660; conducted between July 2018 and June 2021) were two prospective, 100-week, multicenter, randomized, double-masked, active-controlled Phase 3 studies in subjects with visual impairment due to DME. The primary objective of the studies was to demonstrate the non-inferiority of brolucizumab to aflibercept in visual outcomes at Week 52. Both studies were conducted in accordance with the International Council for Harmonization E6 Good Clinical Practice Guideline, the Declaration of Helsinki, and all applicable local, state, and federal laws. Study protocols were reviewed and approved by an independent ethics committee or an institutional review board of each participating center. All subjects provided written informed consent prior to the study initiation. The complete inclusion and exclusion criteria have been described previously.[16] Only one eye per subject was included.

Randomization and treatment

Randomization and treatment masking have been described previously.[16] KESTREL was a 3-arm study wherein the subjects were randomized 1:1:1 to receive brolucizumab 3 mg, brolucizumab 6 mg or aflibercept 2 mg. The brolucizumab arms received 5 loading doses at every 6-week intervals (5 x q6w), followed by a q12w dosing until Week 96 in the maintenance phase, with the option to adjust to a every 8-week interval (q8w) if disease activity (DA) was identified at any of the 7 predefined disease activity assessment (DAA) visits (eg, ≥5-letter loss in best-corrected visual acuity [BCVA] with increase in central subfield thickness [CSFT]

compared with the subject's disease status at Week 28) (**Figure 1A, Supplementary File 1**). Brolucizumab subjects who were assigned to q8w dosing during the maintenance phase remained on a q8w interval until the end of the study (EOS) in KESTREL.

KITE was a 2-arm study wherein subjects were randomized 1:1 to receive either brolucizumab 6 mg or aflibercept 2 mg. The brolucizumab arm received 5 x q6w loading doses followed by q12w dosing during the maintenance phase, with an option to adjust to q8w interval if DA was identified at any of the 11 predefined DAA visits. In KITE, at Week 72, based on a one-time disease stability assessment (DSA) by the masked investigator there was an option to extend the treatment interval for brolucizumab 6 mg patients by 4 weeks, i.e., brolucizumab subjects on a q8w interval could be extended to q12w dosing and those on a q12w interval could be extended to q16w dosing (**Figure 1B**). However, if after Week 72, DA was identified at a scheduled treatment visit (according to subject-specific treatment schedule q12w or q16w) the subject was reassigned to a q8w interval. The subjects who were not identified by the masked investigator for the 4-week extension of their treatment intervals continued with their latest treatment frequency considering adjustments according to DAAs (**Supplementary File 1**).

In both studies, the aflibercept 2 mg arm received 5 loading doses at every 4-week interval (5 x q4w) followed by a fixed q8w dosing till the EOS. (**Figures 1A and 1B**). To maintain masking, DAAs and DSAs (in KITE only) were performed in both brolucizumab and aflibercept arms. An independent, masked review of fundus photography, fluorescein angiography and optical coherence tomography (OCT) images for subjects enrolled in each study was performed at a central reading center.

Study endpoints

The primary endpoint was the mean change in BCVA from baseline at Week 52.[16] The endpoints assessed at Week 100 were secondary and included: the mean change in BCVA from baseline at Week 100; average change in BCVA from baseline over the period of Week 88 to Week 100; mean change in central subfield thickness (CSFT) from baseline at Week 100; average change in CSFT from baseline over the period of Week 88 to 100; the observed treatment status at Week 100, the estimated proportion of subjects maintained an q12w interval (KESTREL) and q12w/q16w (KITE) up to Week 100; and the estimated proportion of patients maintained on q12w (KESTREL) and q12w/q16w (KITE) among those who completed the first q12w cycle with no q8w need at Weeks 32 and 36. Other secondary endpoints were the percentage of subjects with (i) CSFT <280 µm, (ii) presence of intraretinal fluid (IRF)/subretinal fluid (SRF), (iii) presence of IRF at each post-baseline visit and (iv) ≥5-, ≥10- and ≥15-letters gain and loss in BCVA, and (v) ≥2 step and ≥3 step improvement in Diabetic Retinopathy Severity Scale (DRSS) at Week 100. Safety endpoints were the incidence of ocular and non-ocular adverse events (AE), serious AEs, and AE of special interests (AESIs; which included intraocular inflammation [IOI, including retinal vasculitis], retinal vascular occlusion and endophthalmitis) through Week 100. Antidrug antibody (ADA) status at baseline and up to Week 100 was also assessed.

Statistical analysis

Full details of statistical analyses preformed in KESTREL and KITE have been published previously.[16] All analyses at Week 100 were descriptive. For the mean change from baseline in BCVA and CSFT, the least squares (LS) mean and standard error (SE) estimates were analyzed using an ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors, and CSFT categories (<450 µm, ≥450 to <650 µm, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors, respectively. Logistic regression was used to calculate the treatment difference for

percentage of subjects with CSFT <280 µm, IRF and/or SRF, IRF and ≥2-step improvement in DRSS and the corresponding 95% confidence intervals (CI) were calculated using the bootstrap method. The estimate for the proportion of subjects with a positive q12w and q12w/q16w treatment status was derived using Kaplan-Meier time-to-event analyses. The impact of COVID-19 was analyzed by subgroup of COVID-19 impact using the ANOVA model.

All efficacy analyses were performed on the full analysis set that included all randomized subjects who received at least one study injection; safety evaluation was performed on the safety set that included all subjects who received at least one study injection.

RESULTS

Subject disposition

In KESTREL, of the 566 subjects (brolucizumab 3 mg, n = 190; brolucizumab 6 mg, n = 189; aflibercept 2 mg, n = 187) randomized, 464 (82.0%) completed the study at Week 100 (brolucizumab 3 mg, n = 157; brolucizumab 6 mg, n = 154; aflibercept 2 mg, n = 153). Of the 360 subjects (brolucizumab 6 mg, n = 179; aflibercept 2 mg, n = 181) randomized in KITE, 299 (83.1%) completed the study at Week 100 (brolucizumab 6 mg, n = 143; aflibercept 2 mg, n = 156). Details of subject disposition and reasons for discontinuation are shown in **Supplementary Figure 1A and 1B.**

Baseline characteristics

The demographic and baseline characteristics have been reported previously and were generally similar across treatment arms in each study (**Supplementary Table 1**).[16] Analysis of baseline characteristics and demographics did not reveal any impact on efficacy or safety outcomes.

Best-corrected visual acuity

The mean change in BCVA at Week 52 (primary endpoint) achieved with brolucizumab 6 mg in both studies were non-inferior to aflibercept and these VA gains were maintained through Week 100. The LS mean change from baseline in BCVA at Week 100 in brolucizumab 6 mg and aflibercept arms were: + 8.8 letters versus +10.6 letters in KESTREL (treatment difference: −1.7 letters; 95% CI: −3.8, 0.4; **Figure 2A**), and +10.9 letters versus +8.4 letters in KITE (treatment difference: 2.6 letters; 95% CI:0.2, 4.9; **Figure 2B**), respectively. In KESTREL, the average change from baseline in BCVA over the period of Week 88 to Week 100 was +8.6 letters for brolucizumab 6 mg and +10.6 letters for aflibercept. In KITE, the average change from baseline in BCVA over the period of Week 88 through Week 100 was +10.8 letters with brolucizumab 6 mg and + 8.7 letters for aflibercept.

The proportion of subjects with ≥5-, ≥10- and ≥15-letter gains from baseline or who reached BCVA ≥84 letters at Week 100 increased markedly from baseline in all treatment arms in both the studies (**Supplementary Table 2**). A similar proportion of subjects had ≥15-letter gains or reached BCVA ≥84 letters in the brolucizumab 6 mg (40.2%) and aflibercept arms (41.2%), while the proportions were relatively lower in the brolucizumab 3 mg arm (35.3%) at Week 100 in the KESTREL study. In KITE, the proportion of subjects who had ≥15-letter gain or who reached BCVA ≥84 letters were 49.7% in the brolucizumab 6 mg arm and 37.6% in the aflibercept arm, but it was not determined if this is a statistically significant difference (**Supplementary Table 2**).

Central subfield thickness

In both studies, the reduction in CSFT achieved at Week 52 was maintained through Week 100 in each treatment arm. In KESTREL, the LS mean change from baseline in CSFT at Week 100

was −172 µm in the brolucizumab 3 mg arm, −173 µm in the brolucizumab 6 mg arm and −170 µm in the aflibercept arm, respectively (**Figure 3A**). The estimated difference in CSFT for brolucizumab 3 mg versus aflibercept was -1 µm (95% CI: −20, 18) and for brolucizumab 6 mg versus aflibercept it was −3 µm (95% CI: −21, 15). In KITE, it appeared that there were larger reductions in CSFT at all time points through Week 100 (apart from Week 36) in the brolucizumab 6 mg arm versus the aflibercept arm, but statistical analyses were not performed. At Week 100, the LS mean change from baseline in CSFT was −202 µm in the brolucizumab arm compared to −173 µm in the aflibercept arm, with an estimated difference of −29 µm (95% CI: −52, −7), favoring the brolucizumab 6 mg arm (**Figure 3B**).

It appeared that compared with aflibercept-treated subjects, a higher proportion of brolucizumab-treated subjects achieved a CSFT <280 µm at Weeks 52 and 100 in both studies, but statistical analyses were not performed. At Week 100, the proportion of subjects with CSFT <280 µm in KESTREL were 57.9%, 63.5% and 51.9% with brolucizumab 3 mg, brolucizumab 6 mg and aflibercept, respectively (**Figure 3C**). The difference between brolucizumab 3 mg and aflibercept was 5.6% (95% CI: −5.2, 15.7); between brolucizumab 6 mg and aflibercept was 11.6% (95% CI: 2.3, 21.6). At Week 100, 62.0% in the brolucizumab 6 mg versus 47.0% in the aflibercept arm achieved a CSFT <280 µm, with a treatment difference of 14.7% (95% CI: 4.2, 24.9) in KITE (**Figure 3C**).

Intraretinal fluid and/or subretinal fluid

In a similar trend to the Week 52 results, at Week 100 in KESTREL, the proportion of eyes with IRF and/or SRF were 45.8% with brolucizumab 3 mg, 41.8% with brolucizumab 6 mg and 54.0% in the aflibercept arm (brolucizumab 6 mg vs aflibercept difference: −12.4%; 95% CI: −22.8, −2.1); in KITE, it was 40.8% in brolucizumab 6 mg arm compared to 56.9% in the aflibercept arm (difference: −16.2%; 95% CI: −26.4, −5.9; **Figure 4A and 4B)**.

Intraretinal fluid

Compared to baseline, a decrease was noted in the proportion of subjects with IRF in both brolucizumab and aflibercept arms at all post-baseline visits in both studies. In KESTREL, 45.8% of subjects in brolucizumab 3 mg, 41.8% in brolucizumab 6 mg compared to 54.0% in aflibercept arm had IRF at Week 100, with a treatment difference in favor of brolucizumab 6 mg vs aflibercept (difference: −12.4%; 95% CI: −22.8, −2.1) (**Supplementary Figure 2A**). In KITE, the proportion of subjects with IRF was 40.8% in the brolucizumab 6 mg arm compared to 56.9% in the aflibercept arm, with a treatment difference of −16.1% (95% CI: −26.3, −5.7) in favor of brolucizumab (**Supplementary Figure 2B**).

Observed treatment status at Week 100

In KESTREL, 32.9% of subjects in the brolucizumab 6 mg arm were maintained on an exclusive q12w dosing interval up to Week 100 immediately after the loading phase. In KITE, overall, 47.5% of subjects in the brolucizumab 6 mg arm were maintained on a ≥q12w dosing interval at Week 100, of whom 24.8% were maintained on a q16w dosing interval.

Predictability of the first q12w dosing interval and the q8w treatment need

The probability (Kaplan-Meier [K-M] estimates) of brolucizumab-treated subjects being maintained on a q12w dosing interval after loading through Week 100 was 44.1% for the brolucizumab 6 mg arm (95% CI for K-M estimate: 35.7, 52.1) in KESTREL and on a q12/q16w dosing interval was 36.8% for the brolucizumab 6 mg arm (95% CI for K-M estimate: 29.1, 44.5) in KITE (**Supplementary Table 3)**. Among the brolucizumab 6 mg-treated subjects who successfully completed the first q12w interval (i.e., had no observed disease activity at Week 32 and Week 36), the probability of remaining on a q12w dosing up to Week 100 increased to

70.2% (95% CI: 58.7, 79.1) in KESTREL, and to 69.6% (95% CI: 57.4, 78.9) for remaining on a q12w/q16w dosing up to Week 100 in KITE (**Supplementary Table 3)**.

In KESTREL, the proportion of subjects with a q8w treatment need as assessed by the investigator was 21.5% in the brolucizumab 6 mg arm and 14.6% the aflibercept arm at Week 96 (last DAA visit in the study). In KITE, the proportion of subjects assessed to have a q8w need was 16.8% in the brolucizumab 6 mg arm and 32.9% in the aflibercept arm at Week 72 (the DSA time point) and 13.4% in brolucizumab 6 mg versus 29.0% in the aflibercept arm at Week 96.

Number of injections

Overall, the median number of active intravitreal injections up to Week 100 was 11 in the brolucizumab-treated arms in KESTREL and 10 in the brolucizumab 6 mg arm in KITE (**Table 1**). With the fixed q8w dosing schedule, the median number of intravitreal injections in the aflibercept arm was 15 in both studies (**Table 1**). The mean number of intravitreal injections up to Week 100 were 10.6, 10.6 and 13 in the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept arms in KESTREL, respectively. In KITE, the mean number of injections was 10.3 in the brolucizumab 6 mg and 13.2 in the aflibercept arm (**Table 1**).

Improvement from baseline in Diabetic Retinopathy Severity Scale

In KESTREL, 32.8% of subjects in the brolucizumab 6 mg arm and 29.3% in the aflibercept arm achieved a ≥2-step improvement in Early Treatment Diabetic Retinopathy Study (ETDRS) DRSS score at Week 100 (brolucizumab 6 mg vs aflibercept difference: 2.2%; 95% CI:−4.0, 8.4) (**Supplementary Figure 3A)**. In KITE, 35.8% of subjects in brolucizumab 6 mg arm versus 31.1% in aflibercept arm (difference: 4.5%; 95% CI, −1.7,10.8) achieved a ≥2-step improvement in ETDRS DRSS score at Week 100 (**Supplementary Figure 3B**). A ≥3-step improvement in

ETDRS DRSS score at Week 100 was observed in 23.7% of subjects in the brolucizumab 6 mg arm and 22.3% in aflibercept arm (difference: 0.4%; 95% CI, −5.7, 6.8) in KESTREL, and in 21.0% of subjects in the brolucizumab 6 mg arm and 16.9% in aflibercept arm (difference: 3.9%; 95% CI, −2.3,10.0) in KITE (**Supplementary Figure 3A and 3B**).

Safety outcomes

The overall rates of ocular and non-ocular AEs up to Week 100 were similar between brolucizumab and aflibercept arms within each study (**Table 2).** The most frequently (≥2%) reported ocular AEs in the KESTREL and KITE studies are reported in **Table 2 and Table 3**. In KESTREL, 12 subjects (6.3%) in the brolucizumab 3 mg, 8 (4.2%) in brolucizumab 6 mg and 3 (1.6%) in the aflibercept arm had ocular AEs that were considered related to the study treatment. The majority of the ocular AEs were mild to moderate in severity. In KESTREL, 4.2% of subjects in the brolucizumab 3 mg arm, 2.6% in the brolucizumab 6 mg arm and 3.7% in the aflibercept arm had at least 1 severe ocular AE. In KITE, 3.4% of subjects in the brolucizumab 6 mg arm and 2.2% in the aflibercept arm had at least 1 severe ocular AE in the study eye. Overall, 3.7% of subjects in the brolucizumab 3 mg, 1.6% in the brolucizumab 6 mg arm and 1.1% in aflibercept arm in KESTREL and, 2.8% of subjects in the brolucizumab 6 mg arm and 2.2% in the aflibercept arm in KITE discontinued the study treatment due to an ocular AE.

The incidence of ocular and non-ocular SAEs was comparable between the arms in KESTREL and KITE (**Table 2**). There were 19 deaths reported in KESTREL (4 [2.1%] in the brolucizumab 3 mg arm, 8 [4.2%] in the brolucizumab 6 mg arm, and 7 [3.7%] in the aflibercept arm), and 22 deaths were reported in KITE (13 [7.3%] in the brolucizumab 6 mg arm and 9 [5.0%] in the aflibercept arm). None of the deaths were suspected to be related to study treatment by the investigator.

Intraocular inflammation (including retinal vasculitis)

The overall rates of IOI up to Week 100 were 5.3% (n = 10; 6 males, 4 females), 4.2% (n = 8; 4 males, 4 females]), and 1.1% (n = 2; 1 male,1 female) in the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept arms in KESTREL, respectively. In KITE, IOI was reported in 2.2% (n = 4; 1 male, 3 female) of subjects in the brolucizumab 6 mg arm and in 1.7% (n = 3; 1 male, 2 female) in the aflibercept arm **(Table 2).** Three subjects developed an initial IOI event during Year 2 (Week 52 to Week 100) in KESTREL, with 1 subject each in the brolucizumab 3 mg arm (uveitis, mild), brolucizumab 6 mg arm (iridocyclitis, mild), and aflibercept arm (anterior chamber flare, moderate). In KITE, 1 subject in the brolucizumab 6 mg arm (uveitis, mild) developed an initial IOI event in Year 2.

Taking both trials together, there were a total of 40 IOI events associated with brolucizumab (24 events in 10 subjects in the brolucizumab 3 mg arm; 16 events in 12 subjects in the pooled brolucizumab 6 mg arms) during the 100-week study period. Half of the IOI events (20 of 40; 50%) occurred within the first 6 months of the study (11 with brolucizumab 3 mg and 9 with brolucizumab 6 mg); 12 (30%) occurred between 6 and 12 months (8 with brolucizumab 3 mg and 4 with brolucizumab 6 mg) and the remaining 8 (20%) IOI events occurred in Year 2 (5 with brolucizumab 3 mg, 3 with brolucizumab 6 mg). Details on the severe and serious IOI events are provided in **Supplementary File 2**. The median (range) number of brolucizumab injections administered prior to the onset of the first IOI-related AE was 4 (2–9) in the brolucizumab 3 mg arm and 5 (2–12) in the brolucizumab 6 mg arm in KESTREL, and 4 (1–11) in the brolucizumab 6 mg arm in KITE. The median (range) number of days to onset of the first IOI-related event from the last brolucizumab injection was 13 (1–58) in the brolucizumab 3 mg arm and 50 (14–202) in the brolucizumab 6 mg arm in KESTREL, and 33 (2–50) in the brolucizumab 6 mg arm in KITE.

Retinal vasculitis was reported in KESTREL in 3 subjects (1.6%) in the brolucizumab 3 mg arm and 1 subject (0.5%) in the brolucizumab 6 mg arm (**Table 2**). All these AEs occurred in Year 1, and there were no new reports of retinal vasculitis in Year 2 in KESTREL in any treatment arm. There were no cases of retinal vasculitis reported in KITE during the entire study. The incidences of AESIs, reported in Year 1 and Year 2 are shown in **Supplementary Table 4.**

Retinal vascular occlusion

In KESTREL, through Week 100, retinal vascular occlusion was reported in 3 subjects (1.6%) in the brolucizumab 3 mg arm, 3 (1.6%) in the brolucizumab 6 mg arm, and 1 (0.6%) in the aflibercept arm (**Table 2**). Two subjects with retinal vascular occlusion in Year 1 in the brolucizumab 3 mg arm and 1 subject in the brolucizumab 6 mg arm also experienced an IOI event, and these have been described previously.[13] Specifically in Year 2, 5 retinal vascular occlusion events were reported in 4 subjects: 1 in the brolucizumab 3 mg arm, 2 in the brolucizumab 6 mg arm (1 subject had 2 events of retinal vascular occlusion), and 1 in the aflibercept arm. None of these retinal vascular occlusion events reported in Year 2 were associated with IOI (**Supplementary File 2)**.

In KITE, retinal vascular occlusion was reported in 1 subject (0.6%) each in the brolucizumab 6 mg and aflibercept arms, with both events occurring in Year 1 (**Table 2**). No cases of retinal vascular occlusion were reported in Year 2 in KITE. All the images of subjects in KESTREL and KITE were reviewed independently by masked readers at the CRC and no additional cases of IOI, retinal vasculitis or retinal vascular occlusion were identified beyond those reported by the investigators.

Endophthalmitis

Endophthalmitis was reported in 2 subjects (1.1%) in the brolucizumab 3 mg arm and in 1 (0.5%) in the aflibercept arm in KESTREL; no cases of endophthalmitis were reported in Year 2.

No cases of endophthalmitis were reported in the brolucizumab 6 mg arm in KESTREL (**Table 2**). In KITE, endophthalmitis was reported in 2 subjects (1.1%) in the brolucizumab 6 mg arm and 1 subject (0.6%) in the aflibercept arm. In Year 2, 1 new case of endophthalmitis (SAE, severe, culture negative, BCVA of 46 letters at start of event and 77 letters at resolution of the event [+25 letters compared to baseline]) was reported in the brolucizumab 6 mg arm in KITE. The details of the IOI, retinal vasculitis, retinal vascular occlusion, and endophthalmitis cases reported up to Week 52 have been reported previously.[16]

≥15-letter loss in BCVA at Week 100

In both studies, a small number of subjects lost ≥15 letters at Week 100 from baseline and the adverse events related to the vision loss in each case are provided in **Table 4.** In KESTREL, 10 subjects treated with brolucizumab lost ≥15 letters (6 [3.2%] in the 3 mg arm, 4 [2.1%] in the 6 mg arm), 7 of whom lost ≥30 letters. In the brolucizumab 3 mg arm, 1 subject lost 73 letters at Week 100 due to endophthalmitis and retinal detachment, 1 subject experienced retinal arterial occlusion and lost 69 letters and 1 subject lost 63 letters due to retinal vein thrombosis and iridocyclitis. Two subjects lost >30 letters (34 and 38 letters respectively) following 10 and 5 missed study visits respectively with no concurrent ocular adverse events. In the brolucizumab 6 mg arm, 1 subject experienced two events of retinal artery and vein occlusions, iris neovascularization and increased IOP and lost 78 letters compared with baseline and one further subject lost 63 letters following adverse events of Iridocyclitis, cataract and vitreous detachment. In the aflibercept arm, 2 subjects (1.1%) lost ≥15 letters and none lost ≥30 letters. In KITE, 4 subjects (2.2%) in the brolucizumab 6 mg arm lost ≥15 letters, 1 of whom lost ≥30 letters due to a retinal artery occlusion (-75 letters). Six subjects (3.3%) in the aflibercept arm lost ≥15 letters, 2 of whom lost ≥30 letters at Week 100 compared with baseline. One of these subjects developed cataract and lost 77 letters and the other also developed cataract, optic atrophy and missed 2 visits and lost 32 letters.

Antidrug antibodies

In KESTREL, 42 subjects each in the brolucizumab 3 mg arm and brolucizumab 6 mg arm had induced or boosted ADA titers. Of these, 10 subjects (23.8%) in the brolucizumab 3 mg arm and 8 (19.0%) in the brolucizumab 6 mg arm had AESIs. Among the 141 subjects in the brolucizumab 3 mg arm and 139 subjects in the brolucizumab 6 mg arm who were either ADA-negative or had no boost, 2 subjects (1.4%) in each arm had AESIs. In KITE, 27 subjects in the brolucizumab 6 mg arm had induced or boosted ADA titers; of these 2 subjects (7.4%) had AESIs. Among 146 subjects who were either ADA-negative or had no boost, 4 (2.7%) had AESIs.

Impact of COVID-19

There was an impact of the COVID-19 pandemic on the number of protocol deviations. In KESTREL, overall, 41.1% (n = 78), 38.6% (n = 73) and 35.8% (n = 67) subjects had a protocol deviation due to a “missed visit” in the brolucizumab 3 mg, the brolucizumab 6 mg and aflibercept 2 mg arms, respectively. In all, 26.3% (n = 50), 15.3% (n = 29) and 23.5% (n = 44) of subjects in the brolucizumab 3 mg, brolucizumab 6 mg and the aflibercept 2 mg arms, respectively, had protocol deviation “missed active treatment” due to COVID-19. In KITE, overall, 34.1% (n = 61) in the brolucizumab 6 mg arm and 36.5% of subjects in the aflibercept 2 mg arm (n = 66) had a protocol deviation due to a “missed visit”, and 20.1% (n = 36) of subjects in the brolucizumab 6 mg arm and 30.9% (n = 56) in the aflibercept 2 mg arm had a protocol deviation “missed active treatment” due to COVID-19. However, efficacy and safety results were consistent between COVID-19 impacted and non-impacted subgroups.

DISCUSSION

Consistent with the Year 1 findings, the 100-week results of KESTREL and KITE studies demonstrated long-term efficacy and durability of brolucizumab in improving visual and anatomical outcomes in patients with DME. The non-inferior VA gains achieved with brolucizumab 6 mg at Week 52 were maintained over 100 weeks and were comparable to aflibercept in both studies.

The VA gains observed at Week 100 in KESTREL and KITE are consistent with those reported in the pivotal Phase 3 trials RIDE (+10.9 letters) and RISE (+11.9 letters) with ranibizumab, VIVID (+9.4 letters) and VISTA (+11.1 letters) with aflibercept, and YOSEMITE (+10.7 letters) and RHINE (+10.9 letters) with faricimab.[19-21] It is important to highlight that KESTREL and KITE used a q6w loading regimen for brolucizumab (versus standard q4w dosing interval). The rationale of using a q6w loading was based on the results from the Phase 1/2 study which demonstrated that the peak effect of brolucizumab 6 mg on BCVA gains and CSFT reduction was at Week 6 (unpublished data). These results were further substantiated in the Phase 3 HAWK and HARRIER studies for nAMD showing that sustained disease control was achieved during the loading phase, with a substantial proportion of subjects then remaining on a q12w treatment interval during the maintenance phase.[13]

Multiple analyses have identified the presence of IRF to be an important biomarker for disease activity and long-term outcomes in exudative retinal diseases, including nAMD and DME. Specifically, persistence of IRF has been associated with worse BCVA gains in subjects with DME.[22] In both KESTREL and KITE, there was a trend toward a smaller proportion of brolucizumab-treated versus aflibercept-treated patients having IRF in the central 1 mm of macula at Week 100, but this trend was not statistically significant. In addition, it appeared that a greater proportion of subjects achieved a CSFT of <280 µm at Week 52 and Week 100, but it is not known if this is a real difference or due to chance.

The durability of brolucizumab 6 mg with up to q16w intervals was demonstrated in both studies through Year 2. In KITE, 47.5% of subjects achieved a q12w/q16w interval with 24.8% of subjects on a q16w dosing at Week 100. In KESTREL, 32.9% of subjects were maintained on q12w dosing interval up to Week 100. It is important to note that these subjects were maintained on an exclusive q12w regimen (KESTREL) and q12/q16w regimen (KITE) immediately after the loading phase. These proportions may be even higher in the real world as there is more flexibility in treatment regimens than in clinical trials. There was no option to extend to a q16w interval in KESTREL, and once assigned to q8w, brolucizumab subjects remained on this interval until the end of the study. In KITE, the opportunity to extend the treatment interval to a q16w interval was allowed only once, at Week 72. Moreover, as per the study protocol, if a DAA visit was missed for any reason, the treatment interval was automatically switched to q8w on the visit when active treatment should be dispensed in both KESTREL and KITE. Due to the COVID-19 pandemic, there were a number of missed DA visits which had an impact on the observed treatment interval status at Week 100. Furthermore, ~70% of brolucizumab 6 mg subjects who successfully completed the first q12w cycle after the loading phase had the probability of being maintained on an exclusive q12w (in KESTREL) and q12/q16w (KITE) dosing interval up to Week 100, further demonstrating an important durability signal with brolucizumab. Taken together, within this Phase 3 program, brolucizumab 6 mg was found to be 12–16% more effective in resolution of IRF and/or SRF and provided faster and sustained disease control even with extension of dosing intervals up to q16w compared to aflibercept in DME, as already demonstrated in the HARRIER and HAWK trials in nAMD.[13]

The only other agent that has demonstrated q16w durability in a robust, prospective DME trial is the bi-specific antibody, faricimab.[23] In the Phase 3 YOSEMITE and RHINE trials, ~60% of subjects in the faricimab personalized treatment arm (PTI) were on a q16w interval at Week

96.[24] The dosing interval could be reduced/ maintained/ extended by 4 weeks depending on the PTI algorithm.[25, 26] Interestingly, the median number of faricimab injections in the PTI arms (Total 11 injections; [Year 1: 8; Year 2: 3]) were similar to that for brolucizumab in KESTREL (Total 11 injections [Year 1: 7; Year 2: 3]) and KITE (Total 10 injections [Year 1: 7; Year 2: 3]).[21, 25]

The IOI rates with brolucizumab 6 mg in KESTREL and KITE were similar to those reported in the HAWK and HARRIER trials for nAMD.[13] Overall, through Week 100, the IOI rates were 5.3% in the brolucizumab 3 mg arm and 4.2% in the brolucizumab 6 mg arm in KESTREL and, 2.2% in the brolucizumab 6 mg arm in KITE. In the aflibercept 2 mg arm, the IOI rates were 1.1% in KESTREL and 1.7% in KITE. The majority (~56%) of the IOI events in the brolucizumab 6 mg arm occurred within 0-6 months (9 events in 6 subjects) and approximately 20% of IOI events (3 events in 3 subjects) were reported in Year 2. Overall, through Week 100, 3 IOI events (~19%%) in 2 subjects were categorized as severe in the brolucizumab 6 mg arm, all in the KITE study, and there were no severe IOI events in the brolucizumab 6 mg arm in KESTREL.

Due to the confirmed safety signal of retinal vasculitis and/or retinal vascular occlusions, typically occurring in the presence of IOI, there is greater potential for severe, permanent vision loss during treatment with brolucizumab versus aflibercept, therefore continued vigilance and monitoring for any signs of IOI-related events with prompt and intensive management is recommended.[15, 27] Four cases of retinal vasculitis (3 in the brolucizumab 3 mg arm; 1 in the brolucizumab 6 mg arm) were reported in Year 1 in KESTREL (and these cases have been described previously[16]), with no new cases of retinal vasculitis reported in Year 2. In addition, retinal vascular occlusion was reported in 3 subjects in the brolucizumab arms in Year 2 in KESTREL. Two cases were severe, with subjects experiencing ≥30 letters VA loss compared to baseline. None of the retinal vascular occlusion events from Year 2 were associated with IOI

according to the investigators. In KITE, no cases of retinal vasculitis were reported throughout the study, and no new retinal vascular occlusion cases were reported in Year 2. No further cases, other than those identified by the treating investigator, of retinal vasculitis/retinal vascular occlusion were identified through the systematic, prospective imaging analyses of all subjects, conducted by the masked reading center. This supports the perspective that investigators were well informed and vigilant with monitoring of the safety signal associated with brolucizumab.

The retinal vasculitis and retinal vascular occlusion AEs that can occur with brolucizumab are considered to be immune-mediated adverse drug reactions. In a small *in vitro* study, high ADA titers and memory T-cell activation were observed in blood samples of subjects with nAMD who had experienced retinal vasculitis and/or retinal vascular occlusion AEs after exposure to brolucizumab.[28,29] In KESTREL and KITE, the incidence of AESIs were numerically higher in subjects with boosted ADA titers than in subjects who were ADA-negative/had no boost. However, >80% of subjects who had positive boosted or induced ADA status did not experience AESIs; therefore, ADA positivity cannot specifically predict the occurrence of AESI.

There were limitations in KESTREL and KITE: these studies were powered to assess efficacy and not safety, therefore real-world data on the safety of brolucizumab in patients with DME are needed. As per the study design, the dosing interval between the brolucizumab and aflibercept arms was different, thus limiting a direct head-to-head comparison. Moreover, no extension was allowed in brolucizumab patients who were assigned to q8w due to disease activity in KESTREL and during Year 1 in KITE. The study discontinuation rates and study treatment discontinuation rates are quite high for both KESTREL & KITE and ‘subject decision’ was a major contributor to these numbers. Notably, COVID-19 became highly prevalent during the studies and patients may no longer have wanted the additional commitment to a clinical trial during the early stages of the pandemic.

In conclusion, the global, double-masked Phase 3 trials KESTREL and KITE are the only studies to thoroughly evaluate a series of q6w loading doses in the management of DME. Through Week 100, brolucizumab 6 mg, dosed up to q16w, demonstrated clinically meaningful VA gains compared to aflibercept. Although not tested for statistical significance, there were also greater anatomic improvements, manifested as improved IRF, compared to aflibercept, with the overall safety profile of brolucizumab remaining unchanged.

CRediT AUTHOR STATEMENT:

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Data availability statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the program in line with applicable laws and regulations. This study data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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FIGURE LEGENDS

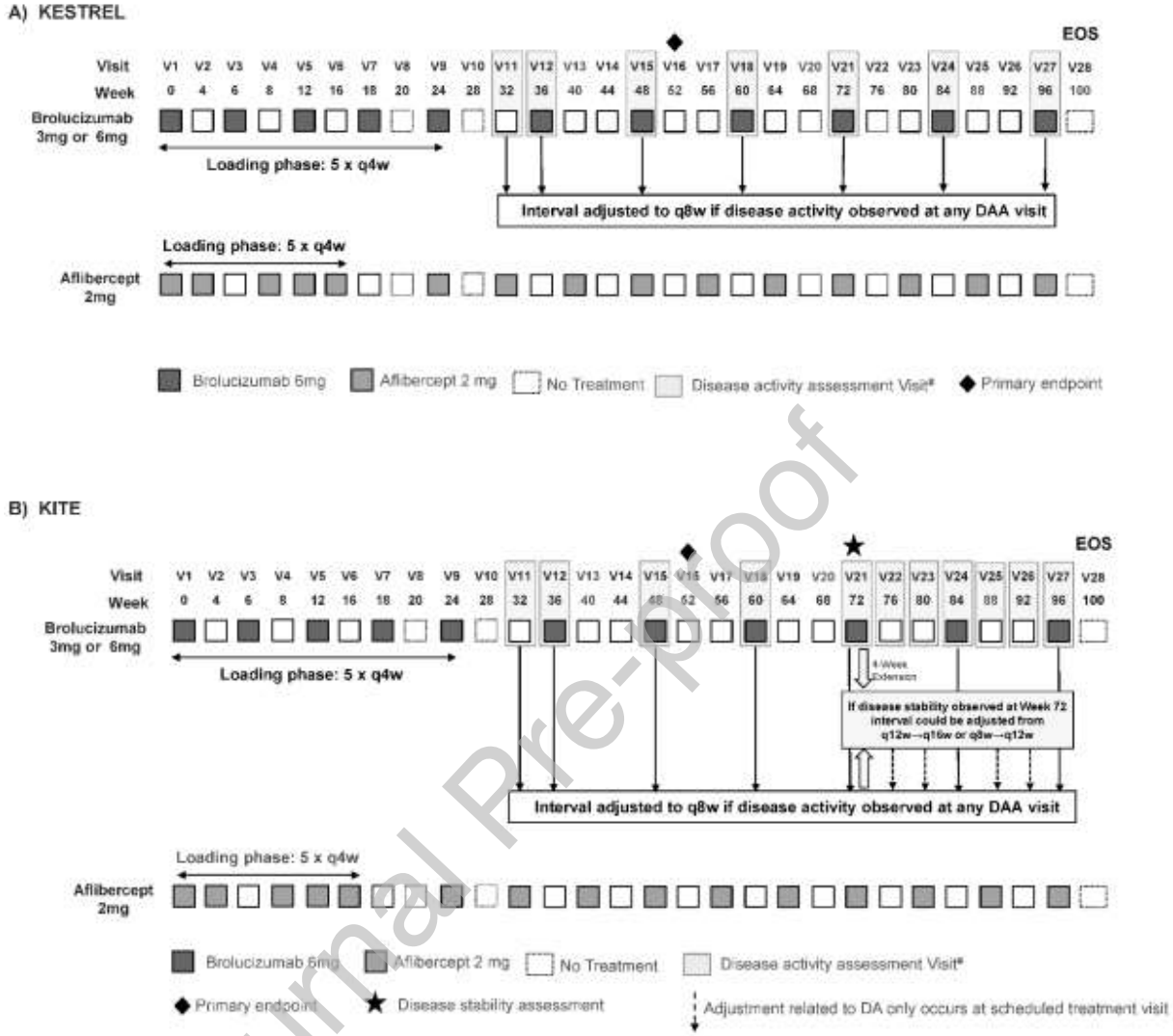


Figure 1. A) KESTREL study design **B)** KITE study design**.**
#Disease activity assessments were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to all injections. DAA, Disease activity assessment; EOS, end of study; q4w, 4-week dosing interval; q6w, 6-week dosing interval; q8w, 8-week dosing interval;

q12w, 12-week dosing interval.

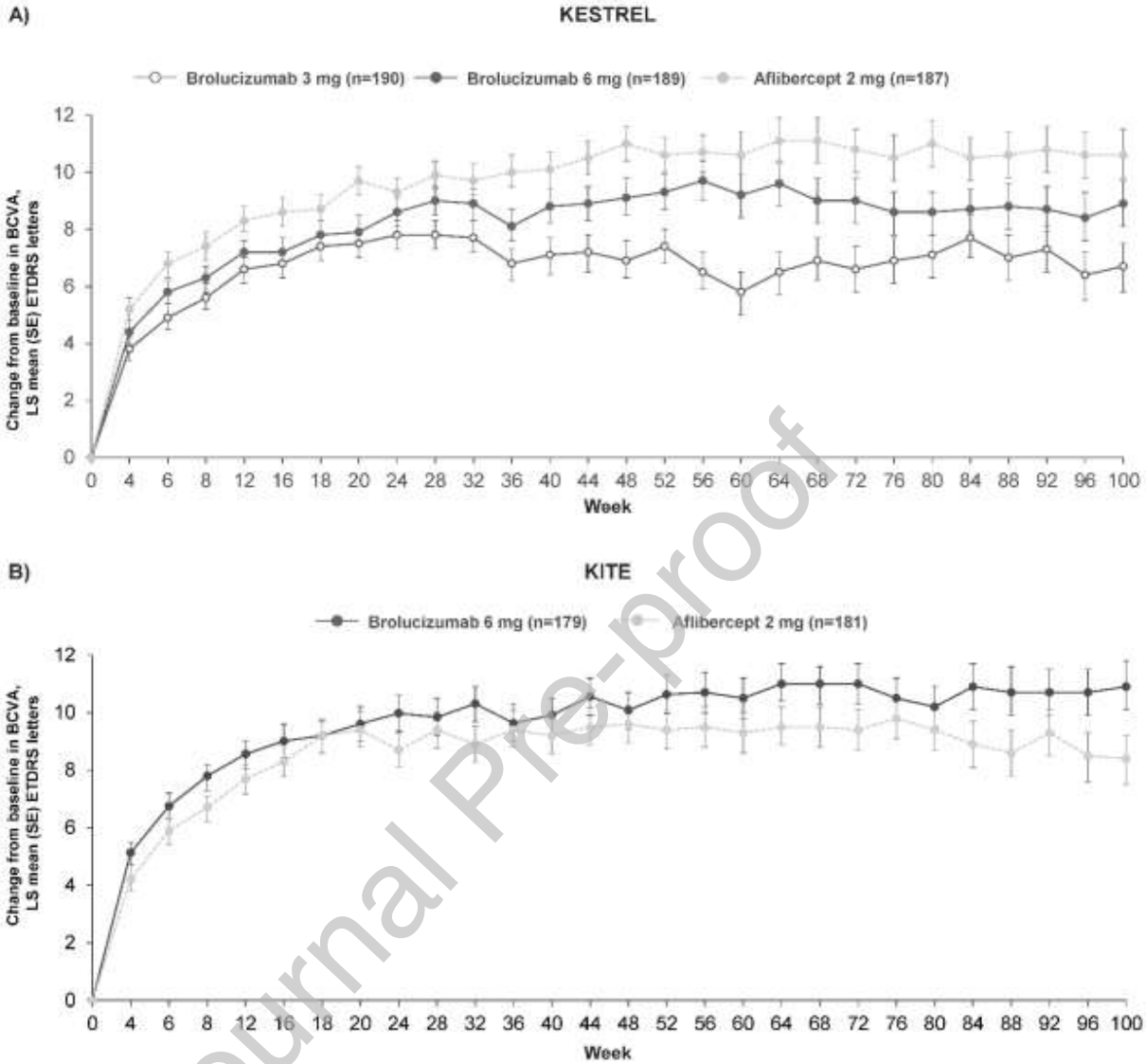


Figure 2. Mean change from baseline in BCVA through Week 100 **A)** KESTREL and **B)** KITE Full analysis set LOCF. LS mean differences in BCVA (brolucizumab–aflibercept, Δ) in KESTREL (−1.7; 95% CI −3.8,0.4) and KITE (2.6; 95% CI 0.2, 4.9). LS mean and SE estimates are analysed using ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65,≥65 years) and treatment as fixed effect factors. BCVA, best corrected visual acuity; BRO, brolucizumab; CI, confidence interval; ETDRS, Early treatment diabetic retinopathy study; LOCF, last observation carried forward; LS, least squares; SE, standard error; VA, visual

acuity.

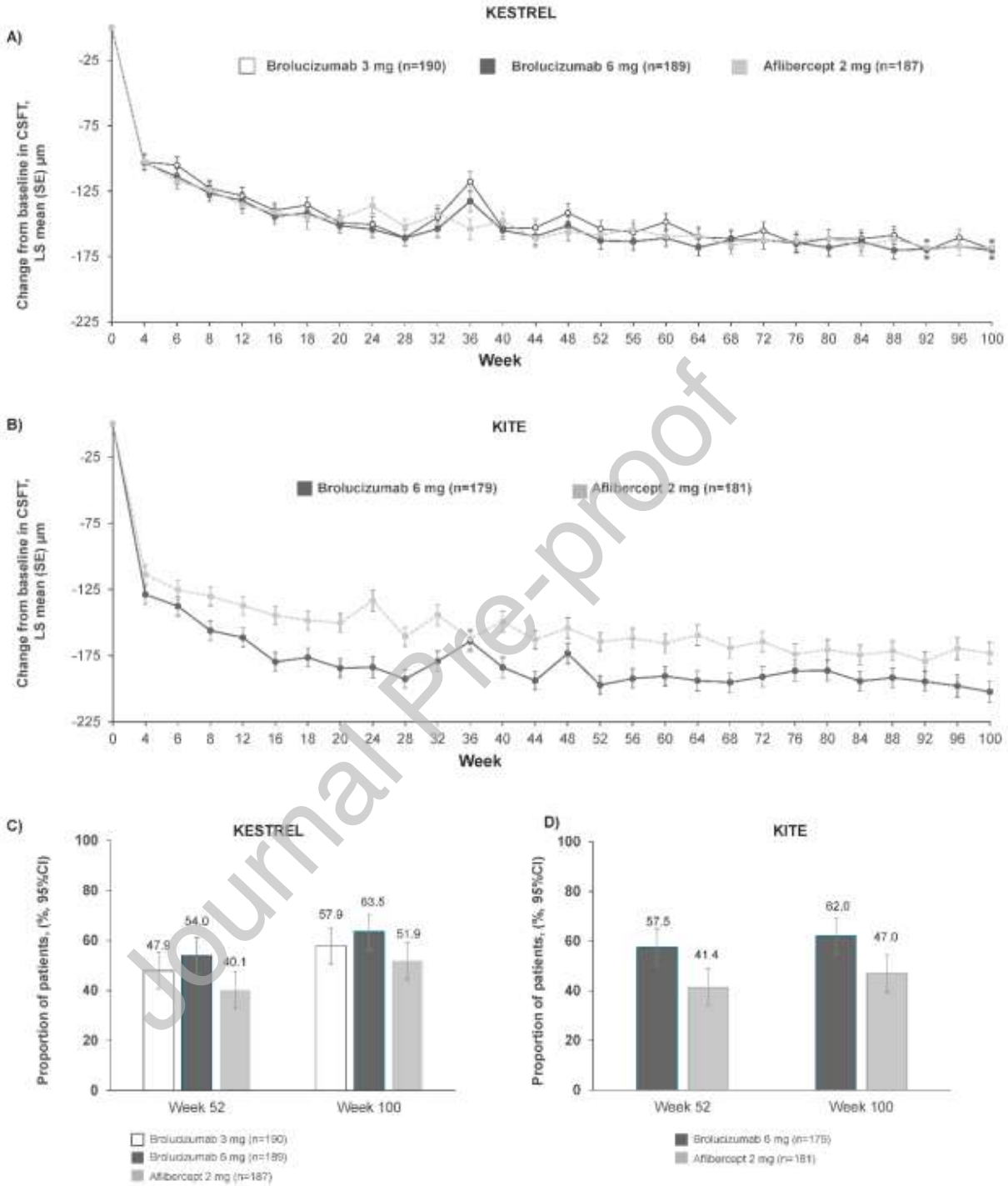


Figure 3. Mean change from baseline in CSFT through Week 100 in **A)** KESTREL and **B)** KITE and **C)** the proportion of subjects with CSFT <280 µm at Week 52 and Week 100
A) and B) Full analysis set LOCF. LS mean differences in CSFT (brolucizumab–aflibercept, Δ) in KESTREL (Brolucizumab 6 mg arm: −3.5 µm; 95% CI: −20.7, 13.8) and KITE (−23.2 µm; 95% CI: −43.5, −3.0). LS mean and SE estimates based on an ANOVA model with baseline, CSFT categories (<450 µm, ≥450–<650 µm; ≥650 µm), age categories (<65,≥65 years) and

treatment as fixed effect factors.CI, confidence interval; CSFT, central subfield thickness; LS, least squares; LOCF, last observation carried forward; SE, standard error. C) Full analysis set LOCF. Statistical model using logistic regression adjusting for baseline CSFT categories (<450, ≥450–<650, ≥650), age categories (<65,≥65 years) and treatment as fixed effect factors. 95% CI calculated using bootstrap method. Median number of injections at Week 52 and Week 100 reported. CI, confidence interval; CSFT, central subfield thickness. LOCF, last observation carried forward.

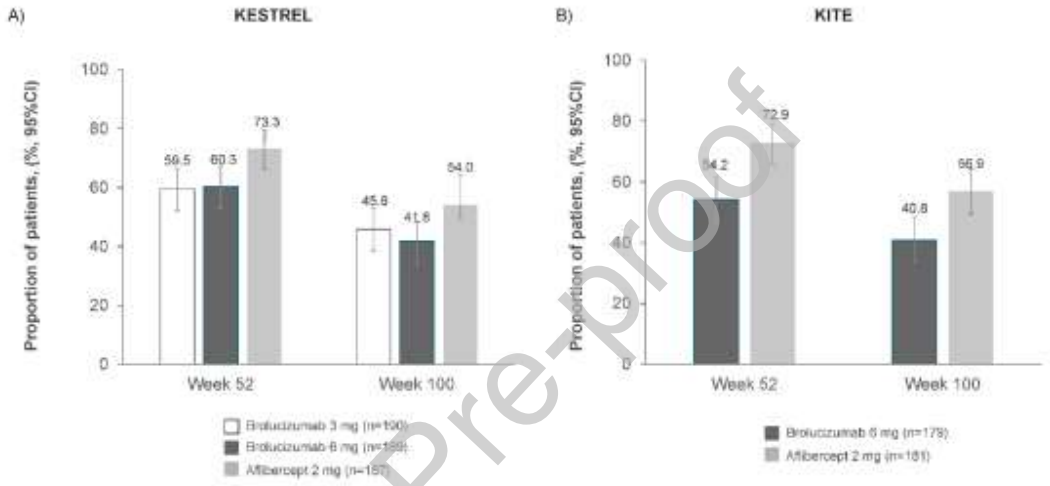


Figure 4. Proportion of patients with IRF and/or SRF present at Week 52 and Week 100 in **A)** KESTREL and **B)** KITE.
Full analysis set LOCF. Statistical model using logistic regression adjusting for baseline fluid status (SRF and/or IRF), age categories (<65,≥65 years) and treatment as fixed effect factors. 95% CI calculated using bootstrap method. Median number of injections at Week 52 and Week 100 reported. IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

Table 1: Number of active injections in each treatment arm in KESTREL and KITE

	KESTREL			KITE	
Number of active injections	**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)**
In Year 1 (Baseline 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
In Year 2 (Week 52 to Week 96)					
Mean (SD)	4.5 (1.2)	4.4 (1.2)	5.3 (1.3)	3.8 (1.3)	5.2 (1.3)
Median	5	4	6	4	6
Total (Baseline to Week 96)					
Mean (SD)	10.6 (3.2)	10.6 (3.0)	13.0 (3.2)	10.3 (2.8)	13.2 (3.1)
Median	11.0	11.0	15.0	10.0	15.0

Treatment interval was fixed for aflibercept arm; hence the number of injections is as expected as per the design of the studies.
Abbreviations: SD, standard deviation

Table 2: Overall safety profile of brolucizumab and aflibercept through Week 100 in KESTREL and KITE

	KESTREL			KITE	
Adverse Event	**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)**

Patients with ≥1 AE, n (%)*	103 (54.2)	92 (48.7)	94 (50.3)	73 (40.8)	74 (40.9)
Ocular (study eye)	146 (76.8)	146 (77.2)	143 (76.5)	136 (76.0)	141 (77.9)
Nonocular					
Patients with ≥1 serious AE, n (%)*	8 (4.2)	7 (3.7)	5 (2.7)	5 (2.8)	3 (1.7)
Ocular (study eye)	48 (25.3)	53 (28.0)	54 (28.9)	48 (26.8)	58 (32.0)
Nonocular					
Patients with ≥15 letter loss from baseline at Week 100, n (%)†	6 (3.2)	4 (2.1)	2 (1.1)	4 (2.2)	6 (3.3)
Death, n (%)	4 (2.1)	8 (4.2)	7 (3.7)	13 (7.3)	9 (5.0)
AEs of special interest (study eye), n (%)					
Endophthalmitis	2 (1.1)	-	1 (0.5)	2 (1.1)	1 (0.6)
Intraocular inflammation[a]	10 (5.3)	8 (4.2)	2 (1.1)	4 (2.2)	3 (1.7)
- including Retinal vasculitis[a]	3 (1.6)	1 (0.5)	-	-	-
Retinal vascular occlusion	3[+] (1.6)	3[#] (1.6)	1 (0.5)	1[b] (0.6)	1[b] (0.6)

Medical Dictionary for Regulatory Activities Version 24.1 (KESTREL) and 24.0 (KITE) 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 patient with multiple occurrences of an AE for a preferred term or system organ class was counted only once in each specific category.[a] Percentages of patients with intraocular inflammation and percentages of patients with retinal vasculitis cannot be added up. [b]No patient with both Retinal vascular occlusion and IOI in KITE
Safety Analysis Set; [†] Full Analysis Set-LOCF; [+] 2 patients also experienced IOI; # 1 patient also experienced IOI
Abbreviations: AE, adverse event; LOCF, last observation carried forward

Table 3: Ocular adverse events (≥ 2% frequency) by treatment arms in KESTREL and KITE

	KESTREL			KITE	
Preferred term n (%)	**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	103 (54.2)	92 (48.7)	94 (50.3)	73 (40.8)	74 (40.9)
Conjunctival hemorrhage	19 (10.0)	16 (8.5)	19 (10.2)	8 (4.5)	6 (3.3)
Cataract	17 (8.9)	16 (8.5)	13 (7.0)	12 (6.7)	19 (10.5)
Intraocular pressure increased	14 (7.4)	11 (5.8)	3 (1.6)	6 (3.4)	4 (2.2)
Diabetic retinal oedema	12 (6.3)	9 (4.8)	4 (2.1)	2 (1.1)	3 (1.7)
Dry eye	10 (5.3)	6 (3.2)	5 (2.7)	9 (5.0)	9 (5.0)
Vitreous detachment	9 (4.7)	10 (5.3)	3 (1.6)	0	1 (0.6)
Punctate keratitis	8 (4.2)	3 (1.6)	1 (0.5)	0	2 (1.1)
Vitreous floaters	7 (3.7)	10 (5.3)	6 (3.2)	4 (2.2)	4 (2.2)
Keratitis	0	4 (2.1)	3 (1.6)	-	-
Visual acuity reduced	7 (3.7)	3 (1.6)	9 (4.8)	6 (3.4)	6 (3.3)
Retinal exudates	7 (3.7)	1 (0.5)	3 (1.6)	3 (1.7)	2 (1.1)
Vision blurred	6 (3.2)	3 (1.6)	1 (0.5)	1 (0.6)	5 (2.8)
Conjunctivitis	4 (2.1)	6 (3.2)	1 (0.5)	6 (3.4)	1 (0.6)
Eye pain	3 (1.6)	6 (3.2)	5 (2.7)	6 (3.4)	4 (2.2)
Posterior Capsule opacification	3 (1.6)	6 (3.2)	3 (1.6)	2 (1.1)	3 (1.7)
Eye Irritation	3 (1.6)	5 (2.6)	4 (2.1)	2 (1.1)	1 (0.6)

Iridocyclitis	4 (2.1)	2 (1.1)	0	3 (1.7)	0
Ocular hypertension	4 (2.1)	2 (1.1)	2 (1.1)	1 (0.6)	0
Uveitis	4 (2.1)	2 (1.1)	0	3 (1.7)	2 (1.1)
Conjunctival hyperemia	4 (2.1)	0	1 (0.5)	0	1 (0.6)
Eye pruritus	-	-	-	5 (2.8)	0
Blepharitis	3 (1.6)	4 (2.1)	4 (2.1)	2 (1.1)	4 (2.2)
Vitreous hemorrhage	2 (1.1)	4 (2.1)	3 (1.6)	2 (1.1)	4 (2.2)

Medical Dictionary for Regulatory Activities Version 24.1 (KESTREL) and 24.0 (KITE) used for the reporting of adverse events. AEs with start date on or after the date of first study treatment administration are counted. AEs started after the subject discontinued study treatment and started alternative DME treatment in the study eye are censored. Preferred terms are sorted by descending frequency in the Brolucizumab 6 mg arm. A subject with multiple occurrences of an AE for a preferred term is counted only once in each specific category. Abbreviations: AE, adverse event.

Table 4. Reasons for ≥15-letter loss at last visit or at Week 100 compared with baseline

Study/treatment arm		Adverse event(s) related to vision loss (preferred term)	BCVA at baseline, ETDRS letters	Last BCVA (vs baseline), ETDRS letters
KESTREL				
1	Bro 3 mg	Endophthalmitis; retinal detachment	78	5 (−73)
2	Bro 3 mg	Retinal arterial occlusion	69	0 (−69)
3	Bro 3 mg	Retinal vein thrombosis; iridocyclitis	72	9 (−63)
4	Bro 3 mg	Missed 5 consecutive visits due to systemic events and died after Week 64	56	18 (−38)
5	Bro 3 mg	Cataract and missed 10 visits in total due to COVID-19 and systemic events	69	35 (−34)
6	Bro 3 mg	Cataract; vitritis	72	43 (−29)
7	Bro 6 mg	2 events of retinal artery and vein occlusions; iris neovascularization; increased IOP	78	0 (−78)
8	Bro 6 mg	Iridocyclitis; cataract; vitreous detachment	74	11 (−63)
9	Bro 6 mg	Disease progression with systemic event and worsened glycemic control	74	58 (−16)
10	Bro 6 mg	Only received 2 consecutive loading doses for the entire study; cataract	70	55 (−15)

11	Afl 2 mg	Endophthalmitis; retinal detachment	29	0 (−29)
12	Afl 2 mg	Treatment interruption due to cardiac failure congestive	77	61 (−16)
KITE				
1	Bro 6 mg	Retinal artery occlusion	75	0 (−75)
2	Bro 6 mg	Missed 10 visits in total due to COVID-19; vitreous hemorrhage	53	25 (−28)
3	Bro 6 mg	Iridocyclitis; uveitis	73	57 (−16)
4	Bro 6 mg	Iridocyclitis; vitreous opacities	66	50 (−16)
5	Afl 2 mg	Cataract	77	0 (−77)
6	Afl 2 mg	Cataract; optic atrophy and missed 2 consequent visits due to systemic events	64	32 (−32)
7	Afl 2 mg	Missed 7 visits in total due to COVID-19; cataract	50	28 (−22)
8	Afl 2 mg	Missed 8 visits in total due to COVID-19	68	51 (−17)
9	Afl 2 mg	Cataract	67	51 (−16)
10	Afl 2 mg	Missed 12 visits in total due to COVID-19 and systemic events	71	56 (−15)

The number of subjects included in analysis: Brolucizumab 3mg, n = 190; Brolucizumab 6 mg, n = 189; Aflibercept, n = 187 in KESTREL; Brolucizumab 6 mg, n = 179; Aflibercept, n = 181 in KITE. Medical Dictionary for Regulatory Activities Version 24.1 (KESTREL) and 24.0 (KITE) used for the reporting of adverse events.
Abbreviations: BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study.

Supplementary Files

Supplementary File 1

Disease Activity Assessment (DAA) and Disease Stability Assessment (DSA)

DAAs

The DAAs were performed to allocate brolucizumab subjects according to the individual treatment needs to either every 12 weeks (q12w) or every 8 weeks (q8w) treatment schedule. In KESTREL, the DAAs were performed at Weeks 32, 36, 48, 60, 72, 84, and 96. In KITE, the DAAs were performed Weeks 32, 36, 48, 60, 72, and at every visit from Week 72 through Week 96. In both studies, Weeks 32 and 36 were the

2 DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arms, to ensure that subjects with high treatment need were identified early on.

The DAA was at the discretion of the masked investigator and was based on changes in the vision and anatomical parameters with reference to subject's disease status at Week 28. The outcome of this assessment was captured as,

- "q8w-need": identified disease activity which according to the masked investigator requires more frequent anti-VEGF treatment, eg ≥5 letters loss in BCVA (compared to Week 28), which, based on anatomical parameters, is attributable to DME disease activity.
- "no q8w-need": Otherwise.

If DAA revealed a need for a more frequent dosing, the subjects were switched to a q8w treatment and remained on the same interval till end of study in KESTREL, and until Week 72 in KITE. If a subject missed any of the following DAA visits (Weeks 36, 48, 60, 72, 84), the brolucizumab subject was assumed to have had a "q8w-need" at this missed visit and was assigned to a q8w schedule at the next visit (ie, at the next visit the subject will receive an active injection). To maintain masking, DAAs were conducted on all subjects in both treatment arms.

DSA (only in KITE)

The DSA was a one-time assessment performed at Week 72 in KITE to evaluate the potential for treatment interval extension. Subjects were assessed by the masked investigator for the option to extend their current treatment interval by 4 weeks (i.e., extend subjects on a q12w treatment to q16w and subjects on q8w to q12w). Only

brolucizumab subjects who demonstrated disease stability at Week 72 were considered for treatment interval extension. The outcome of this assessment was captured as:

- "**Extension of treatment interval":** if according to the masked investigator there was sufficient disease stability to justify an extension of the treatment interval by 4 weeks, (eg, the subject showed no disease activity during the last 2 DAAs, at Week 60 and Week 72).
- "**No extension of treatment interval"**: otherwise

The subjects who were not identified by the masked investigator for the 4-week extension of their treatment intervals continued with their latest treatment frequency considering adjustments according to DAAs. To evaluate the adequacy of the individualized q8w, q12w, or q16w treatment intervals, DAAs were performed at every visit from Week 72 up to and including Week 96 (i.e., every 4 weeks) and subjects had their treatment interval modified accordingly. If after Week 72, disease activity had been identified by the masked investigator at a scheduled treatment visit (according to the subject specific treatment schedule q12w or q16w), the subject was assigned to q8w treatment schedule.

Impact of DAA and DSA on Treatment Schedule in KITE					
Treatment schedule before week 72	**DSA at week 72**	**Treatment schedule after week 72**	**DAA visits with option to adjust to q8w**		**DAA visits without the option to adjust to q8w**
q12w	4-Week interval extension	q16w	Weeks 76, 92		Weeks 80, 84, 88, 96
	No extension	q12w	Weeks 84, 96		Weeks 76, 80, 88, 92
q8w	4-Week interval extension	q12w	If last active injection was at Week 64	Weeks 76, 88	Weeks 80, 84, 92, 96

		q12w	last active injection was at Week 68	Weeks 80, and 88	Weeks 76, 84, 88, 96
	No extension	q8w	n.a		

Supplementary File 2

Severe and serious IOI events

In KESTREL, there were total 5 severe IOI events reported in 3 subjects in brolucizumab 3 mg arm and 4 of these events occurred during the first 6 months of the study; there were no severe IOI events reported in brolucizumab 6 mg arm. In KITE, 3 IOI events in 2 subjects in brolucizumab 6 mg arm were considered as severe and all of them occurred during the first 6 months of the study. Similarly, in KESTREL, there were

total 6 IOI events in 3 subjects in the brolucizumab 3 mg group that were considered as serious and 4 of these occurred during the first 6 months; there were no serious IOI events reported in brolucizumab 6 mg arm. In KITE, only 1 IOI event in a subject in brolucizumab 6 mg arm was adjudged as serious and occurred during the first 6 months of the study.

Retinal artery occlusion – cases reported with brolucizumab in Year 2

KESTREL: The subject in the brolucizumab 3 mg arm was a male, had retinal artery occlusion (severe) and mild atrial fibrillation and was hospitalized on Day 672 (after having received 10 intravitreal injections and 76 days after the last active injection). No anterior chamber cells/flares and vitreous haze was observed, FA revealed central retinal artery occlusion. Both the events were ongoing at the time of study completion. The BCVA score was 0 (finger count) at the time of event and remained so at study completion. The investigator did not suspect the retinal vascular occlusion event to be related to either the study treatment or study procedure. In the brolucizumab 6 mg arm, 2 subjects had retinal vascular occlusion. One male subject experienced decreased vision on Day 408 (after 9 intravitreal injections and 19 days since last active injection). On Day 411, the subject was diagnosed with severe cerebrovascular accident, retinal artery occlusion and retinal vein occlusion (severe) and was hospitalized. Study treatment was discontinued; the BCVA score at time of event was 32 letters (−46 letters versus baseline). The subject had multiple episodes of increased intraocular pressure during the study. The events (retinal artery occlusion and retinal vein occlusion) were ongoing at the time of study completion. The investigator assessed the events as suspected to be related to the study medication. The other event in the brolucizumab 6

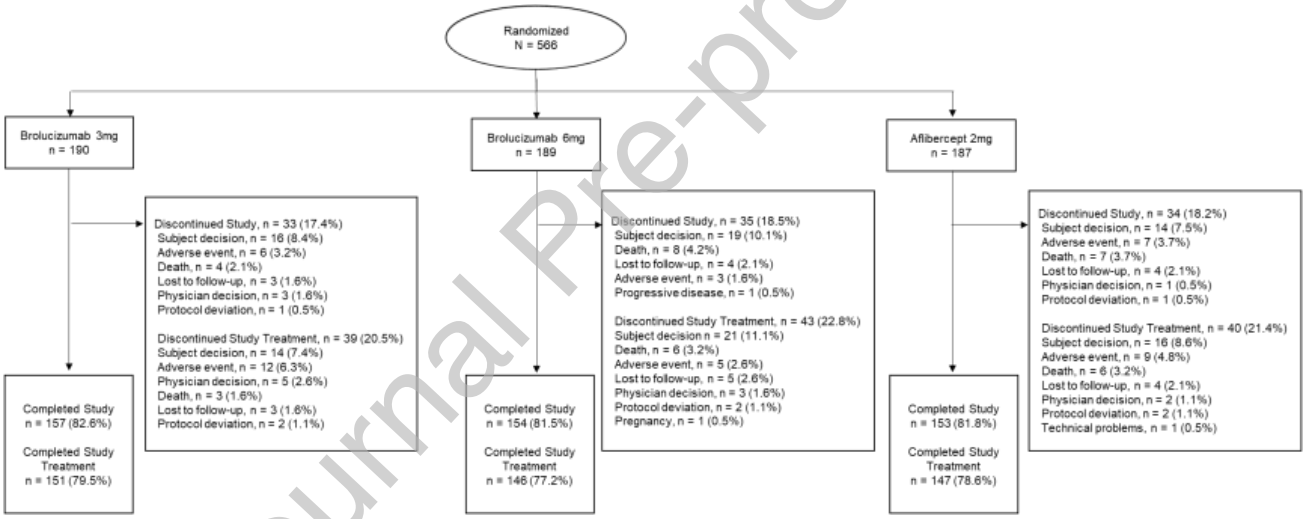
mg group was reported in a male patient, who experienced retinal artery stenosis (mild) on Day 200 (after 3 intravitreal injections and 26 days since last active injection). No action was taken on the study medication and the subject completed the study. The BCVA at time of the event was 53 letters (+19 letters versus baseline) and 70 letters (+36 letters versus baseline) at the end of study. The event was ongoing at the time of study completion. The investigator did not suspect the event to be related to the study medication.

No cases of retinal vascular occlusion reported in Year 2 in KITE

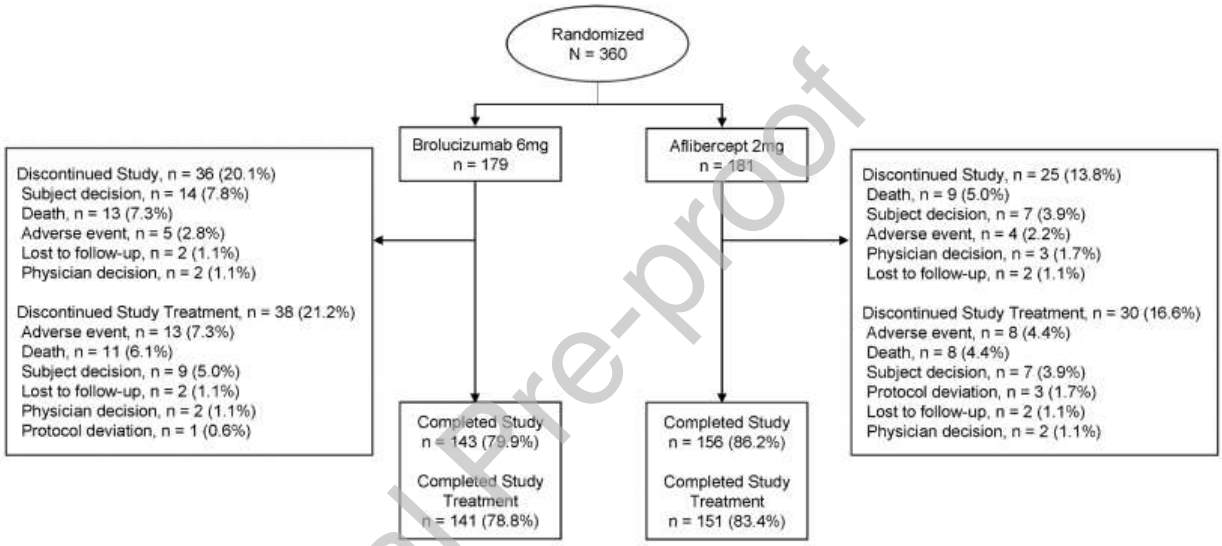
Supplementary Figures

Supplementary Figure 1. Subjection disposition in (A) KESTREL and (B) KITE

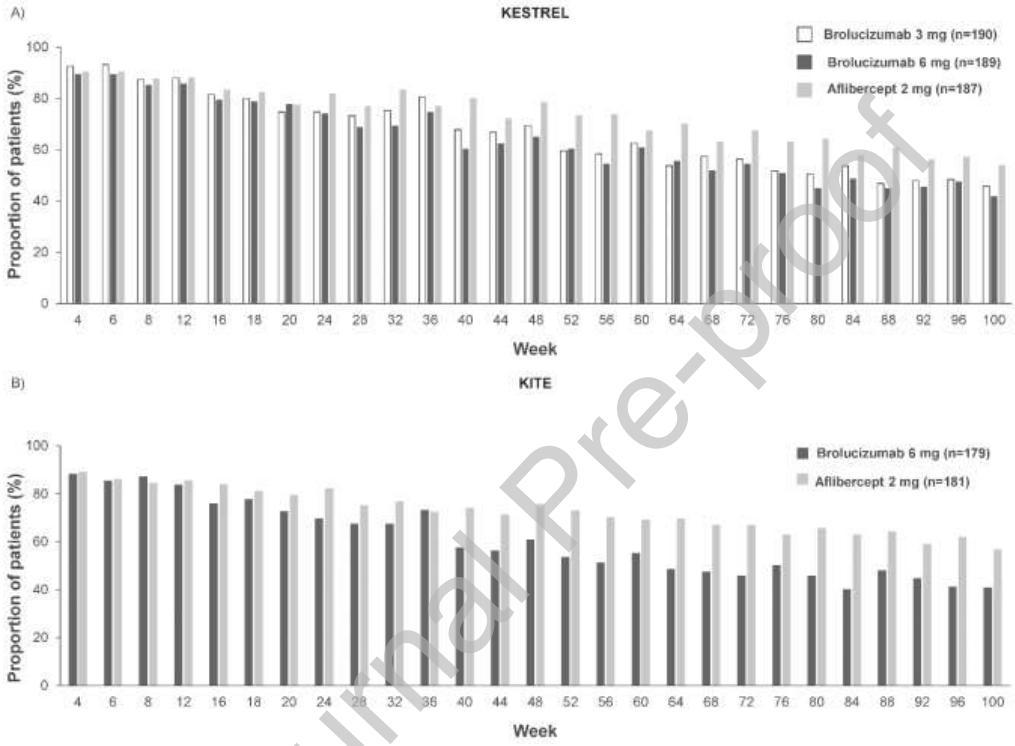
A) KESTREL



B) KITE



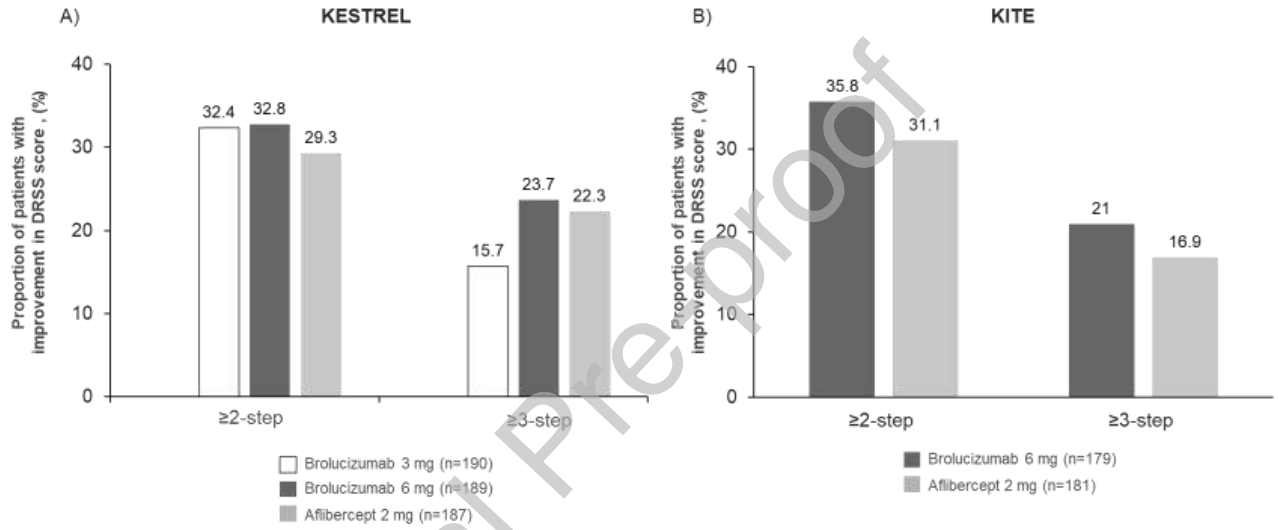
Supplementary Figure 2: Proportion of subjects with presence of IRF in the study eye by visit



Full analysis set LOCF. Statistical model using logistic regression adjusting for age categories (<65, ≥65 years) and treatment as fixed effect factors.

Abbreviations: IRF, intraretinal fluid; LOCF, last observation carried forward

Supplementary Figure 3. Proportion of subjects with ≥2-step and ≥3-step improvement from baseline in ETDRS Diabetic Retinopathy Severity Scale at Week 100



Supplementary Table 1. Baseline characteristics

	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 (9.8)	62.4 (10.1)	63.9 (10.1)	62.3 (10.6)	62.2 (9.5)
<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)
Male, n (%)	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	0	0	0	9 (5.0)	10 (5.5)
Vietnamese	0	0	0	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 (1.16)	7.69 (1.07)	7.44 (1.13)	7.55 (1.17)	7.46 (1.16)
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 (30.8)	9.4 (19.5)	9.6 (24.2)	10.4 (16.6)	9.9 (20.7)
BCVA (letters), mean (SD)	65.7 (11.1)	66.6 (9.7)	65.2 (12.4)	66.0 (10.8)	63.7 (11.7)

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
11- Advanced PDR	0	0	0	0	1 (0.6)
12- Very advanced PDR	0	0	0	0	0

A subject can have multiple races; Diabetes type is based on primary diagnosis; Percentages (%) are calculated based on n. n values are only provided where these differ from the overall N values. '-' indicates term not present in relevant Clinical Study Report. 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

Supplementary Table 2. Number and proportion of subjects who gained ≥5, ≥10 and ≥15 ETDRS letters in BCVA from baseline or reached ≥84 letters at Week 100 in the study eye

	KESTREL			KITE	
Week 100, n (%)	**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**
≥5-letter gain from baseline or reached BCVA of ≥84 letters	131 (68.9%)	137 (72.5%)	143 (76.5%)	138 (77.1%)	133 (73.5%)
≥10-letter gain from baseline or reached BCVA of ≥84 letters	96 (50.5%)	105 (55.6%)	112 (59.9%)	110 (61.5%)	98 (54.1%)
≥15-letter gain from baseline or reached BCVA of ≥84 letters	67 (35.3%)	76 (40.2%)	77 (41.2%)	89 (49.7%)	68 (37.6%)

Full analysis set-LOCF

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; LOCF, last observation carried forward

Supplementary Table 3. Kaplan-Meier estimates for q12w dosing maintenance and q8w treatment status need at Week 100

	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 (KESTREL) and q12w-q16w interval (KITE) after loading to Week 100, %	33.4%	44.1%	N.A	36.8%	N.A
Subjects remaining on q12w at Week 100 within those who successfully completed the first q12w cycle at Week 36*, %	61.3%	70.2%	N.A	69.6%	N.A
Proportion of subjects with a q8w need at Week 96, (%)	23.0%	21.5%	14.6%	13.4%	29.0%

*Censored: subjects are considered to no longer be under risk for a q8w-need identification at later visits

Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are 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.

Supplementary Table 4. Adverse events of special interest reported in KESTREL and KITE, by year

	KESTREL			KITE	
AEs of special interest (study eye), n (%)	**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)**
Baseline to Week 52 (Year 1)					
Endophthalmitis	2 (1.1)	-	1 (0.5)	1 (0.6)	1 (0.6)
Intraocular inflammation[a]	9 (4.7)	7 (3.7)	1 (0.5)	3 (1.7)	3 (1.7)
- including Retinal vasculitis[a]	3 (1.6)	1 (0.5)	-	-	-
Retinal vascular occlusion	2 (1.6)	1 (0.5)	-	1[b] (0.6)	1[b] (0.6)
Week 52 to Week 100 (Year 2)					
Endophthalmitis	-	-	-	1 (0.6)	-
Intraocular inflammation[a]	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.6)	-
- including Retinal vasculitis[a]	-	-	-	-	-
Retinal vascular occlusion	1 (0.5)	2 (1.1)	1 (0.5)	-	-

n refers to number of subjects who developed at least 1 adverse event of special interest in each category

[a] Percentages of patients with intraocular inflammation and percentages of patients with retinal vasculitis cannot be added up. [b]No patient with both retinal vascular occlusion and IOI in KITE. Abbreviations: AE, adverse event; IOI, intraocular inflammation

Table of contents statement

The Phase 3 KESTREL & KITE studies compared the efficacy and safety of brolucizumab with aflibercept in patients with diabetic macular edema. Through Week 100, brolucizumab 6 mg, dosed up to q16w, demonstrated clinically meaningful vision gains and greater anatomic improvements compared to aflibercept, with an overall favorable benefit/risk profile. Brolucizumab could therefore provide an additional therapeutic option in DME that reduces the burden on patients, physicians, and the health care system.