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ORIGINAL RESEARCH

Efficacy and Safety of Brolucizumab, Aflibercept, and Ranibizumab for the Treatment of Patients with Visual Impairment Due to Diabetic Macular Oedema: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction: Key clinical guidelines recommend anti-vascular endothelial growth factor (VEGF) therapy as first-line treatment for visual impairment due to diabetic macular oedema (DMO). A systematic literature review (SLR) and network meta-analysis (NMA) were conducted comparing the relative efficacy of the anti-VEGF brolucizumab with a focused network of the most relevant comparator dosing regimens approved in countries other than the USA (aflibercept, ranibizumab). The safety and tolerability of brolucizumab were also assessed.

Methods: A broad SLR was conducted to identify randomised controlled trials to ensure all relevant potential comparators were captured. Identified studies were refined to those appropriate for inclusion in the NMA. A Bayesian NMA was conducted comparing brolucizumab 6 mg (every 12 [Q12W]/every 8 weeks [Q8W]) with relevant aflibercept 2 mg and ranibizumab 0.5 mg regimens.

Results: Fourteen studies were included in the NMA. At 1-year follow-up, the various aflibercept 2 mg and ranibizumab 0.5 mg regimens were mostly comparable with brolucizumab 6 mg Q12W/Q8W across key visual and anatomical outcomes, except brolucizumab 6 mg was favoured over ranibizumab 0.5 mg every 4 weeks (Q4W) for the change from baseline (CFB) in best-corrected visual acuity (BCVA), and BCVA loss/gain of pre-specified numbers of letters, and over ranibizumab 0.5 mg pro re nata for CFB in diabetic retinopathy severity scale, and retinal thickness. At year 2, where data were available, brolucizumab 6 mg showed similar results across efficacy outcomes versus all other anti-VEGFs. In most cases, discontinuation rates (all cause, and due to adverse events [AE]) and serious and overall rates of AEs excluding ocular

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inflammatory events were similar (in unpooled and pooled-treatment analyses) versus comparators.
Conclusion: Brolucizumab 6 mg Q12W/Q8W was comparable or superior to aflibercept 2 mg and ranibizumab 0.5 mg regimens for various visual and anatomical efficacy outcomes and discontinuation rates.

Keywords: Aflibercept; Anti-VEGF; Best-corrected visual acuity; Brolucizumab; Diabetic macular oedema; Diabetic retinopathy; Network meta-analysis; Ranibizumab; Retinal thickness; Visual impairment

Key Summary Points

Diabetic macular oedema (DMO) leads to progressive retinal dysfunction and if left untreated, irreversible vision loss. The disease affects 5.47% of patients with diabetes, globally.

Across key clinical guidelines, anti-vascular endothelial growth factor (VEGF) therapies, administered via intravitreal (IVT) injection, are recommended as first-line treatment for patients with visual impairment due to DMO. The efficacy and safety of the anti-VEGF brolucizumab for this indication has been investigated by two phase 3 randomised head-to-head studies versus aflibercept (KESTREL and KITE).

The main aim of this study was to compare the relative efficacy of brolucizumab 6 mg via network meta-analysis (NMA) based on a focused network of the most relevant available anti-VEGFs (aflibercept 2 mg, ranibizumab 0.5 mg) approved in a number of countries other than the USA, including the UK; the safety and tolerability of brolucizumab were also assessed.

Brolucizumab 6 mg showed similar efficacy for key visual and anatomic outcomes including best-corrected visual acuity, diabetic retinopathy severity, and retinal thickness outcomes versus the relevant anti-VEGFs. Brolucizumab 6 mg showed an overall favourable benefit/risk profile with comparable rates of discontinuation and serious and overall adverse events to the other anti-VEGFs, except for ocular inflammatory and occlusive events.

This is the first analysis assessing the efficacy and safety of brolucizumab 6 mg for the treatment of patients with visual impairment due to DMO using this focused network of comparators.

INTRODUCTION

Diabetic macular oedema (DMO), a frequent complication of diabetes mellitus, is characterised by abnormal fluid accumulation in the macula [1, 2]. DMO leads to progressive retinal dysfunction [3, 4], and if left untreated can result in permanent and irreversible loss of vision [5]. Vascular endothelial growth factor (VEGF) is a signalling protein that promotes the formation of new blood vessels (angiogenesis), with VEGF-A being a key regulator of this process [6]. Increased levels of signalling through this pathway, resulting from VEGF-A overproduction due to oxidative stress induced by hyperglycaemia, are associated with the characteristics of DMO: pathological ocular angiogenesis and build-up of fluid in the retina (retinal oedema) due to disruption of the blood-retinal barrier (which regulates fluid flow from retinal blood vessels) [7–9]. Secondary to this, hard exudates (composed of lipid and proteinaceous material leaking from the damaged blood vessels) settle in the retina, resulting in retinal thickening [1, 10]. Pathological fluid build-up in DMO is associated with worse visual

outcomes; patients with higher fluid levels have worse visual acuity than those with lower fluid levels [11].

The International Diabetes Federation estimated that there were 536.6 million adults (aged 20–79 years [10.5%]) living with diabetes in 2021, predicted to rise to 783.2 million in 2045 (12.2%) [12]. Among patients with diabetes, the global pooled prevalence of optical coherence tomography (OCT)-diagnosed DMO is estimated to be 5.47% [13]. Over the next 10 years, the population of patients with DMO is expected to grow by approximately 19% [14]. In the UK, in 2021 the prevalence of diabetes was 3,996,000 (8.2%) in adults aged 20–79 years [12]. A UK database analysis estimated the prevalence of DMO among patients with diabetes to be 7.1% in England (2010), with 2.7% of these patients experiencing clinically significant DMO with visual impairment [15]. In a meta-analysis of 35 population-based observational studies in Europe (1996–2016), across the seven UK studies identified, the prevalence of clinically significant DMO was estimated to be higher at 5.2% among patients with diabetes [16]. Approximately 12.7% of patients with DMO have bilateral disease [17].

DMO is the number one cause of blindness among patients with diabetes [18], and typically affects working age adults [19]. Across key guidelines (the International Council of Ophthalmology [20], the American Academy of Ophthalmology [21], the European Society of Retina Specialists [22], the UK consensus working group [23]) and evidence based-recommendations from the National Institute for Health and Care Excellence (NICE) [24–26], anti-VEGF therapy, administered via intravitreal (IVT) injection to the affected eye, is recommended as first-line treatment for patients with DMO.

Licensed anti-VEGF therapies for the management of DMO include brolucizumab [27], aflibercept [28], ranibizumab [29], and most recently, faricimab [30], although available comparators vary by country as off-label bevacizumab may be used in some countries [21, 22].

The efficacy and safety of brolucizumab for the treatment of visual impairment due to DMO has been assessed by two phase 3, 2-year, randomised, double-blind, head-to-head studies (KESTREL and KITE) versus aflibercept [31]. In KESTREL, patients were randomised 1:1:1 to receive brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg (note, the brolucizumab 3 mg dose is not included in the licenced indication [27]). In KITE, patients were randomised 1:1 to receive brolucizumab 6 mg or aflibercept 2 mg. In both trials, brolucizumab was administered as five loading doses (LD) once every 6 weeks (Q6W), with subsequent doses per protocol-specified maintenance schedule i.e. once every 12 weeks, with an option to adjust to once every 8 weeks based on a patient's disease activity at specific disease activity assessment visits (Q12W/Q8W). In KITE, patients receiving brolucizumab also had the option to extend their treatment interval at week 72 by 4 weeks. Aflibercept 2 mg was administered as 5 LD once every 4 weeks (Q4W) with subsequent doses Q8W in both trials.

In the absence of head-to-head phase 3 trial data for brolucizumab versus ranibizumab, and alternative regimens for aflibercept, the aim of this study was to compare the relative efficacy of brolucizumab 6 mg for the treatment of DMO via a network meta-analysis (NMA). A focused network was considered to compare the most relevant available comparators (aflibercept 2 mg, ranibizumab 0.5 mg) approved in countries other than the USA (non-US), including the UK and other European countries. The safety and tolerability of brolucizumab were also assessed.

METHODS

Systematic Literature Review

To identify comparator studies for an NMA assessing the efficacy, safety, and tolerability of anti-VEGFs, including brolucizumab, for the treatment of DMO, a broad systematic literature review (SLR) was performed to ensure all potential comparators were captured. This SLR and NMA are reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [32, 33]. The PRISMA-NMA checklist is provided in Table S1 in the supplementary material.

Identification and Selection of Studies

The Ovid platform was used to search Embase, MEDLINE Daily, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic reviews on 6 December 2021 (Table S2 in the supplementary material). All relevant publications indexed in Embase were identified by the database search strings, which were then modified for performing searches in Medline and the Cochrane Library to account for differences in syntax and thesaurus headings (Tables S3–S5 in the supplementary material).

Hand searching of relevant conference proceedings between 2019 and 2021, relevant clinical trial registries, previous health technology assessment (HTA) submissions, bibliographic reference lists of included studies, relevant SLRs, relevant HTA documents, and other grey literature sources were used as a supplementary measure to ensure all relevant studies were included in the search (further details are provided in Table S6 in the supplementary material).

The pre-specified population, intervention, comparator, outcomes, and study design (PICOS) elements are presented in Table S7 in the supplementary material. Screening against the selection criteria at the title/abstract, and full-text stage was performed by two independent reviewers, with any conflicts resolved by a third, more senior investigator. A record was kept of studies excluded at the full-text stage along with a clear justification for their exclusion. Data from the included publications were extracted by one reviewer into standardised, piloted data extraction tables in Microsoft Excel, with the information checked and validated by an independent internal data check.

All studies were assessed for risk of bias using the NICE checklist for randomised controlled trials (RCTs) [34] and the Jadad scale [35].

Network Meta-Analysis

An NMA was conducted comparing the efficacy of brolucizumab with a focused group of comparators: the anti-VEGFs aflibercept, and ranibizumab. The safety and tolerability of these interventions were also assessed. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Treatments for DMO vary with respect to molecule, dose, and treatment regimen (e.g. frequency of administration). The approved doses (non-US) for comparators included in the NMA were brolucizumab 6 mg, aflibercept 2 mg, and ranibizumab 0.5 mg. Studies reporting Q4W, Q8W, or Q12W/Q8W, and pro re nata (PRN; as needed) dosing regimens were treated as separate treatment nodes for all outcomes. Notably in the KESTREL and KITE trials, following five LD every 6 weeks, the study eyes were placed on a Q12W treatment interval, with the option of adjusting the interval to Q8W if disease activity was detected at any of the predefined assessment visits [31]. In KITE, patients receiving brolucizumab also had an option to extend their treatment interval by 4 weeks (i.e. Q8W to Q12W, or Q12W to every 16 weeks [Q16W]) if disease stability was observed at week 72 (i.e. no disease activity during the last two disease activity assessment visits) [36].

Two alternative approaches were considered for the analysis of all-cause study discontinuation, and for serious ocular, and non-ocular adverse events (AEs): (1) keeping all treatment regimens as separate nodes in the network, and (2) pooling different administration frequencies for the same treatment and dose into a single node (e.g. combining Q4W and Q8W). Molecule-based pooling for aflibercept and ranibizumab was considered appropriate for all-cause study discontinuation, as discontinuation was found not to be statistically significantly affected by regimen characteristics in the NMA conducted by NICE in their clinical guideline for neovascular age-related macular degeneration (nAMD; NG82) [37]. Pooling was also considered appropriate for serious ocular, and non-ocular AEs reported in most trials. Generally, dosing regimens would not influence the incidence of serious AEs except for intraocular inflammation (IOI)-related events, including retinal vasculitis (RV) and retinal vascular occlusion (RO). However, as IOI (including RV) and/or RO were not reported in other trials for

anti-VEGFs in DMO besides KESTREL and KITE [31], they are not included in this NMA. Note that only one potential dosing regimen was available for brolucizumab (not less than 8-week interval during maintenance) so pooling was not applied for this treatment node.

Addition of laser photocoagulation (LP) to a treatment was assumed to constitute a distinct treatment node, irrespective of whether given as part of a prompt or deferred regimen; therefore as per licensing, all combination arms of anti-VEGF and LP were excluded as not being of interest for the current analysis.

The feasibility of performing an NMA at two time points (year 1 and year 2) was assessed. All studies were examined for availability of data for each comparator and outcome of interest, a qualitative assessment of heterogeneity with respect to baseline characteristics was conducted, and an evaluation made of the potential to form a treatment network.

Outcomes of interest for the NMA were the change from baseline in best-corrected visual acuity (BCVA), improvement/worsening in number of Early Treatment Diabetic Retinopathy Study (ETDRS) letters, change from baseline in retinal thickness, diabetic retinopathy severity score (DRSS), and descriptive tolerability.

Statistical Analysis

Pairwise meta-analyses were conducted for each outcome on the basis of a classical (frequentist) approach to assess heterogeneity across studies reporting the same treatment contrasts and were conducted using StataIC 15 and its associated packages (findings not shown). The NMA was conducted using a Bayesian framework and analyses followed NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 guidelines; models were implemented using publicly available WinBUGS code [38].

For continuous outcomes, the mean difference and 95% credible interval (CrI) were calculated. For the proportion of patients experiencing gains or losses of pre-specified numbers of ETDRS letters (e.g. the proportion of patients gaining $\geq$15 letters), referred to as BCVA categorical change, data was synthesised as a series of conditional probabilities, incorporating data on all reported categories of BCVA response using a generalised linear model with a binomial likelihood and a probit link function. There were seven categories for which data were consistently reported in the studies: losing $\geq$15, $\geq$10, or $\geq$5 letters, losing <5 and gaining <5 letters, or gaining $\geq$5, $\geq$10, or $\geq$15 letters and these were regrouped to create mutually exclusive groups of patients, for example, the proportion of patients losing $\geq$15 letters, patients losing <15 and $\geq$10 letters and losing <10 and $\geq$5 letters etc. *Z*-scores and associated 95% CrIs were calculated. Safety and tolerability were analysed as rate data, using the proportion of patients experiencing an event at trial-specific follow-up times. The rate data analysis was implemented using a Poisson likelihood and log link model with the longest follow-up data available from each study included in the analysis and results presented as hazard ratios (HR) and 95% CrI.

Both random effects and fixed effects models were fitted to all outcomes. Models were run for three chains, each with 20,000 iterations after a burn-in of 50,000, and model convergence assessed through the diagnostic plots (including Gelman-Rubin diagnostic [39]). Decisions on the best model fit were based on an approximate difference of deviance information criterion (DIC) $\geq$3 favouring one model over the other, and comparison of the total residual deviance versus the number of datapoints and findings from the direct pairwise analyses. Consistency of direct and indirect evidence in the network was assessed using the approach described by Dias et al. [40].

General Data Analysis

Studies with a follow-up between 48 and 56 weeks were classified as reporting results at year 1, and those with a follow-up between 100 and 108 weeks were classified as year 2; studies reporting time points which did not meet these criteria were excluded. Analyses of change from baseline outcomes were conducted at a specific time point.

For the pooled analyses, where outcomes were discrete (i.e. a count), the arms were pooled by adding the observations together. After pooling, studies reporting only one treatment node were excluded as they provided no information for the analysis.

RESULTS

Identified Publications and Study Characteristics

In total, 140 publications reporting on 44 unique studies were included in the broad SLR. Refining the inclusion of comparators to only licensed doses (in non-US countries) of aflibercept 2 mg, and ranibizumab 0.5 mg reduced the number of studies relevant for inclusion in the NMA to 14, reported in 66 publications (Fig. 1; Table 1). Of note, though the European licences for aflibercept and ranibizumab permit treat and extend (TREX) dosing regimens, no studies with a TREX protocol were deemed suitable for inclusion in the NMA.

A summary by outcome of the trials used to conduct the indirect treatment comparison is provided in Table 1, with baseline patient and disease characteristics provided in Tables S9 and S10 in the supplementary material.

In general, baseline patient characteristics were similar across the included studies, except two studies that included an 100% Asian population [41, 42], and one study that included an

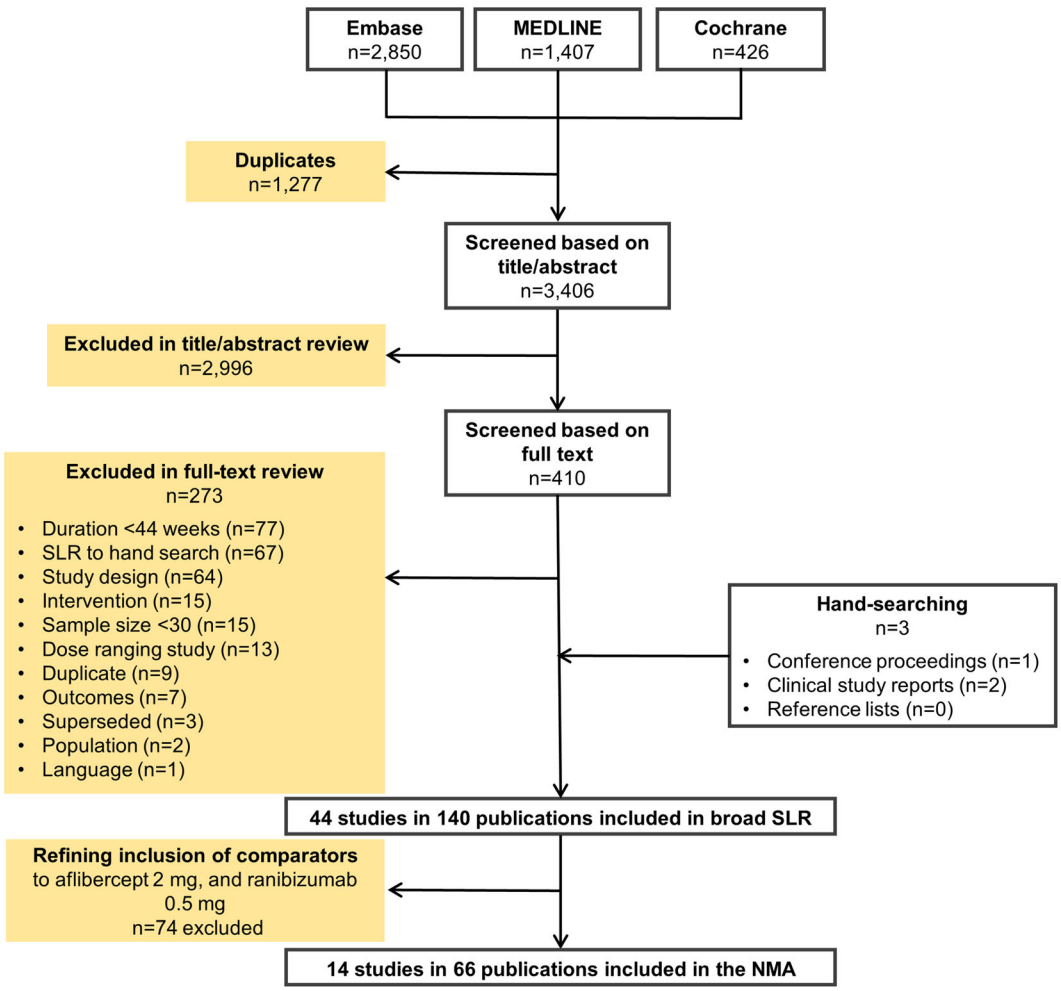

Fig. 1 PRISMA diagram. Abbreviations: NMA, network meta-analysis; SLR, systematic literature review

Table 1 Summary of interventions and outcomes reported for trials included in the indirect treatment comparison[§]

Trial	Treatment	Outcome							
		Mean change in BCVA	Loss or gain of 10 or 15 BCVA letters	Diabetic retinopathy (DRSS step change)	Retinal thickness	Study discontinuation (all-cause)	Study discontinuation (AE)	Serious ocular AEs	Serious non-ocular AEs
Chatzirallis 2020	AFL 2 mg PRN	✔	✗	✗	✗	✗	✗	✔	✗
	RAN 0.5 mg PRN								
DA VINCI	AFL 2 mg Q4W	✔	✔	✗	✗	✔	✔	✔	✗
	AFL 2 mg Q8W								
	AFL 2 mg PRN								
	LP/ LP + placebo/ sham								
KESTREL[¶]	BRO 6 mg Q12W/Q8W	✔	✔	✔	✔	✔	✔	✔	✔
	AFL 2 mg Q8W								
KITE[¶]	BRO 6 mg Q12W/ Q8W[‡]	✔	✔	✔	✔	✔	✔	✔	✔
	AFL 2 mg Q8W								
LUCIDATE	RAN 0.5 mg PRN	✔	✗	✔	✔	✔	✗	✔	✗
	LP/ LP + placebo/ sham								
READ-2	RAN 0.5 mg PRN	✔[†]	✔[†]	✗	✗	✔	✔[†]	✗	✗
	LP/ LP + placebo/ sham								

Table 1 continued

Trial	Treatment	Outcome							
		Mean change in BCVA	Loss or gain of 10 or 15 BCVA letters	Diabetic retinopathy (DRSS step change)	Retinal thickness	Study discontinuation (all-cause)	Study discontinuation (AE)	Serious ocular AEs	Serious non-ocular AEs
Re-Des	RAN 0.5 mg PRN	✔	✗	✗	✗	✔	✗	✔	✗
	LP/ LP + placebo/ sham								
REFINE	RAN 0.5 mg PRN	✔	✔	✔	✔	✔	✔	✔	✔
	LP/ LP + placebo/ sham								
RESPOND	RAN 0.5 mg PRN	✔	✔	✗	✔	✗	✗	✗	✗
	LP/ LP + placebo/ sham								
RESTORE	RAN 0.5 mg PRN	✔	✔	✗	✔	✔	✔	✔	✔
	LP/ LP + placebo/ sham								
REVEAL	RAN 0.5 mg Q4W	✔	✔	✗	✗	✔	✔	✔	✔
	LP/ LP + placebo/ sham								
VISTA[¶]	AFL 2 mg Q4W	✔	✔	✔	✔	✔	✔	✔	✔
	AFL 2 mg Q8W								
	LP/ LP + placebo/ sham								

Table 1 continued

Trial	Treatment	Outcome							
		Mean change in BCVA	Loss or gain of 10 or 15 BCVA letters	Diabetic retinopathy (DRSS step change)	Retinal thickness	Study discontinuation (all-cause)	Study discontinuation (AE)	Serious ocular AEs	Serious non-ocular AEs
VIVID[¶]	AFL 2 mg Q4W	✔	✔	✔	✔	✔	✔	✔	✔
	AFL 2 mg Q8W								
	LP/ LP + placebo/ sham								
VIVID-East	AFL 2 mg Q4W	✔	✔	✔	✗	✔	✔	✔	✗
	AFL 2 mg Q8W								
	LP/ LP + placebo/ sham								
Total	–	13 studies	10 studies	7 studies	8 studies	12 studies	9 studies	12 studies	7 studies

Abbreviations: AE, adverse event; AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; DRSS Diabetic Retinopathy Severity Scale; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab

[†]Although the READ-2 study reported data for several outcomes, this trial was only included in the analysis of all-cause discontinuation as after 6 months, patients in the LP treatment arm were able to receive RAN 0.5 mg or LP, if centre subfield thickness was 250 µm or more; mean number of RAN injections was 4.4 in this group between 6–24 months compared with 5.3 in the RAN 0.5 mg PRN group. This is likely to introduce bias for the outcomes reported

[‡]Patients in KITE had the option to extend from Q12W to Q16W at week 72

[¶]These studies had year 1 and year 2 data

[§]The details of references for each study are available in Table S8 in the supplementary material

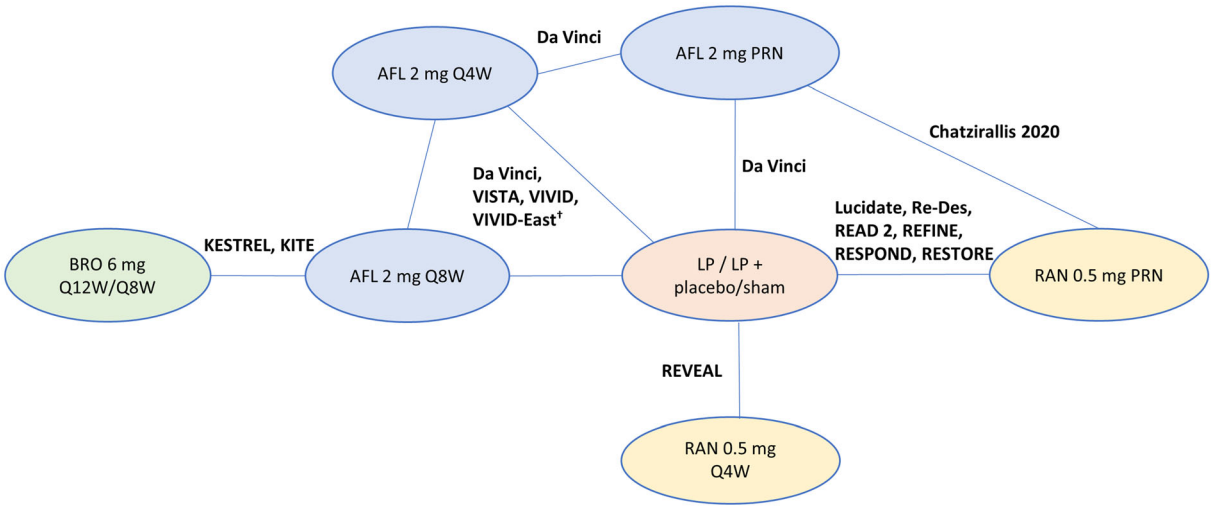

Fig. 2 Network diagram. †All studies report data for all sides of this loop. Note, in KITE, patients receiving brolucizumab had the option to extend their dosing regimen from Q12W to Q16W at week 72. Abbreviations: AFL, aflibercept; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab

Asian majority population (92.3%) [43], while the remaining 11 studies included predominantly white patients. However, clinical opinion suggested it was unlikely that outcomes for these populations would differ significantly, and therefore all three studies in the Asian population were included.

Eight studies reported time since diabetes diagnosis, ranging from approximately 11 to 18 years. Of note, time since diagnosis was much shorter in the REFINE trial at approximately 1 year [42]; however, it was not clear from the publication whether these values referred to duration of diabetes or duration of DMO. In terms of baseline haemoglobin A_{1c} (HbA_{1c}) level, the studies were generally comparable, ranging from 7.23% to 8.08%. All included studies, except Re-Des, reported mean BCVA scores at baseline ranging from 25 to 70 letters. Fewer studies reported baseline retinal thickness, which ranged from 412 µm to 540 µm. The data from these studies used in the NMAs are provided in Tables S11–S14 in the supplementary material.

The risk of bias assessment for individual trials included in the NMA is provided in Table S16 in the supplementary material. Of the 14 studies assessed, 7 were determined to be of high quality (Jadad score of 4–5), 5 of medium quality (Jadad score of 2–3), and 1 of low quality (Jadad score of 0–1) [44], due to insufficient information identified in the publication. VIVID and VISTA trials were assessed together, because these had identical designs.

Trial Data and Evidence Network

The evidence network is presented in Fig. 2. LP was included in order to establish a common comparator that allowed for the indirect comparisons to be made. This was chosen as the reference treatment for the majority of outcomes, as LP was the most 'well-connected' treatment in the network, with the greatest number of studies reporting data. The exception was BCVA outcomes at year 2, where data for LP was not available, and therefore aflibercept 2 mg Q8W was chosen. Outcomes reported in each trial included in the NMA are detailed in Table 1. Not all studies reported data for both time points of interest (i.e. year 1 and year 2 follow-up).

Results of the NMA

Results are presented for each outcome for the best fit model (either fixed or random effects).

Table 2 BCVA outcomes, brolucizumab 6 mg Q12W/Q8W vs comparators

Intervention	Comparator	CFB in BCVA (ETDRS letters) Relative mean difference				BCVA categorical change (gain/loss of pre-specified numbers of ETDRS letters) *Z*-score			
		Year 1 (random effects)		Year 2 (random effects)		Year 1 (fixed effects)		Year 2 (fixed effects)	
		Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)
BRO 6 mg Q12W/Q8W†	LP	***10.22 (6.97, 13.68)***	***10.25 (1.67)***	***9.67 (3.98, 15.59)***	***9.71 (2.80)***	***−0.95 (−1.16, −0.73)***	***−0.95 (0.11)***	***−1.05 (−1.29, −0.80)***	***−1.05 (0.12)***
BRO 6 mg Q12W/Q8W†	AFL 2 mg Q4W	−1.30 (−4.54, 1.97)	−1.30 (1.61)	−0.93 (−6.70, 4.91)	−0.93 (2.81)	0.18 (−0.04, 0.39)	0.18 (0.11)	−0.19 (−0.42, 0.06)	−0.18 (0.12)
BRO 6 mg Q12W/Q8W†	AFL 2 mg Q8W	−0.13 (−2.63, 2.45)	−0.12 (1.25)	0.22 (−3.73, 4.44)	0.26 (1.96)	0.002 (−0.15, 0.15)	0.002 (0.08)	−0.04 (−0.20, 0.11)	−0.04 (0.08)
BRO 6 mg Q12W/Q8W†	AFL 2 mg PRN	1.06 (−3.56, 5.52)	1.04 (2.27)	–	–	0.16 (−0.28, 0.60)	0.16 (0.23)	–	–
BRO 6 mg Q12W/Q8W†	RAN 0.5 mg Q4W	***5.41 (0.61, 10.47)***	***5.45 (2.47)***	–	–	***−0.37 (−0.70, −0.04)***	***−0.37 (0.17)***	–	–
BRO 6 mg Q12W/Q8W†	RAN 0.5 mg PRN	3.63 (−0.20, 7.40)	3.63 (1.89)	–	–	−0.22 (−0.51, 0.06)	−0.23 (0.14)	–	–

Font in bold and italics indicates the intervention is favoured over the comparator

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CFB, change from baseline; Crl, credible interval; ETDRS, Early Treatment Diabetic Retinopathy Study; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; SD, standard deviation

†Patients in KITE had the option to extend from Q12W to Q16W at week 72

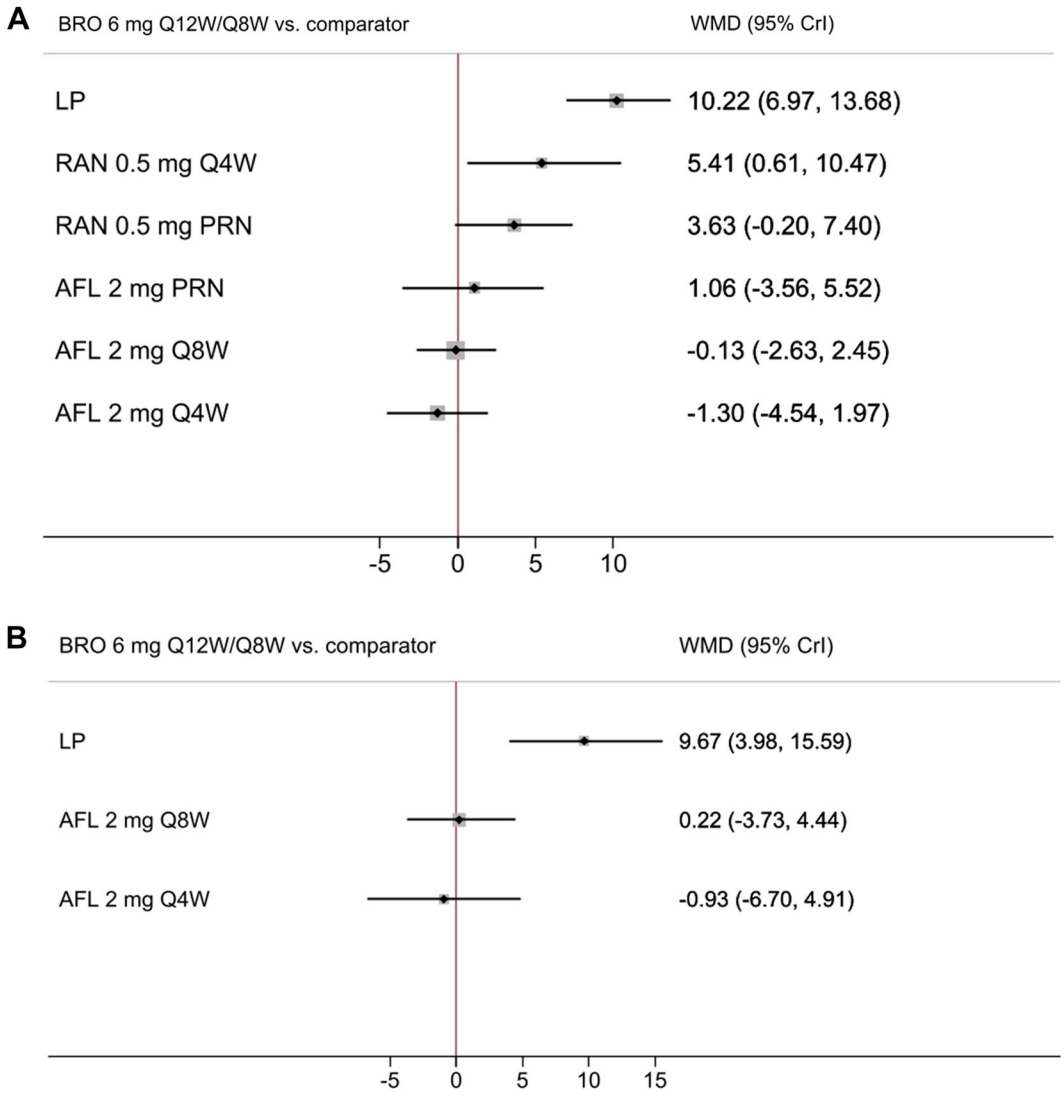

Fig. 3 Forest plot of the change from baseline in BCVA (ETDRS letters) at **A** 1 year and **B** 2 years. Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; Crl, credible interval; ETDRS, Early Treatment Diabetic Retinopathy Study; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; WMD, weighted mean difference

Efficacy Outcomes

Change From Baseline in BCVA (ETDRS Letters)

For the change from baseline in BCVA (ETDRS letters), 13 studies were included in the year 1 analysis, and four studies in the year 2 analysis (Table 1). It was unclear in the Re-Des study [44] which outcome measure was used for BCVA (ETDRS letters, Snellen, or logMAR); however, as a result of the large mean change from baseline value (+8.7 ETDRS letters) and standard deviation ([SD] 9.1 ETDRS letters) for the ranibizumab arm, it was assumed the scale was letters and therefore this study could be included in the analysis. Chatzirallis et al. [45] did not report standard error and this was estimated from the reported *p* value for the

Table 3 Diabetic retinopathy and retinal thickness, brolucizumab 6 mg Q12W/Q8W vs comparator

Intervention	Comparator	≥2-step improvement from baseline in DRSS Odds ratio				CFB in retinal thickness (µm) Relative mean difference			
		Year 1 (fixed effects)		Year 2 (fixed effects)		Year 1 (fixed effects)		Year 2 (fixed effects)	
		Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)	Median (95% Crl)	Mean (SD)
BRO 6 mg Q12W/Q8W†	LP	***5.11 (3.14, 8.36)***	***5.28 (1.34)***	***4.73 (2.81, 8.21)***	***4.93 (1.39)***	***−123.7 (−152.5, −95.41)***	***−123.8 (14.58)***	***−115.6 (−144, −86.83)***	**−115.6 (14.54)**
BRO 6 mg Q12W/Q8W†	AFL 2 mg Q4W	1.14 (0.73, 1.78)	1.17 (0.27)	1.29 (0.82, 2.06)	1.33 (0.32)	−5.11 (−32.89, 23.13)	−5.08 (14.4)	−0.20 (−29.72, 29.51)	−0.21 (15.1)
BRO 6 mg Q12W/Q8W†	AFL 2 mg Q8W	1.27 (0.91, 1.77)	1.29 (0.22)	1.21 (0.88, 1.65)	1.22 (0.20)	−8.82 (−23.01, 5.35)	−8.82 (7.22)	−9.67 (−25.03, 5.71)	−9.67 (7.85)
BRO 6 mg Q12W/Q8W†	RAN 0.5 mg PRN	***3.49 (1.26, 8.47)***	***3.84 (1.89)***	–	–	***−70.67 (−106.2, −35.24)***	***−70.57 (18.09)***	–	–

Font in bold and italics indicates the intervention is favoured over the comparator

Abbreviations: AFL, aflibercept; BRO, brolucizumab; CFB, change from baseline; Crl, credible interval; DRSS, diabetic retinopathy severity scale; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; SD, standard deviation

†Patients in KITE had the option to extend from Q12W to Q16W at week 72

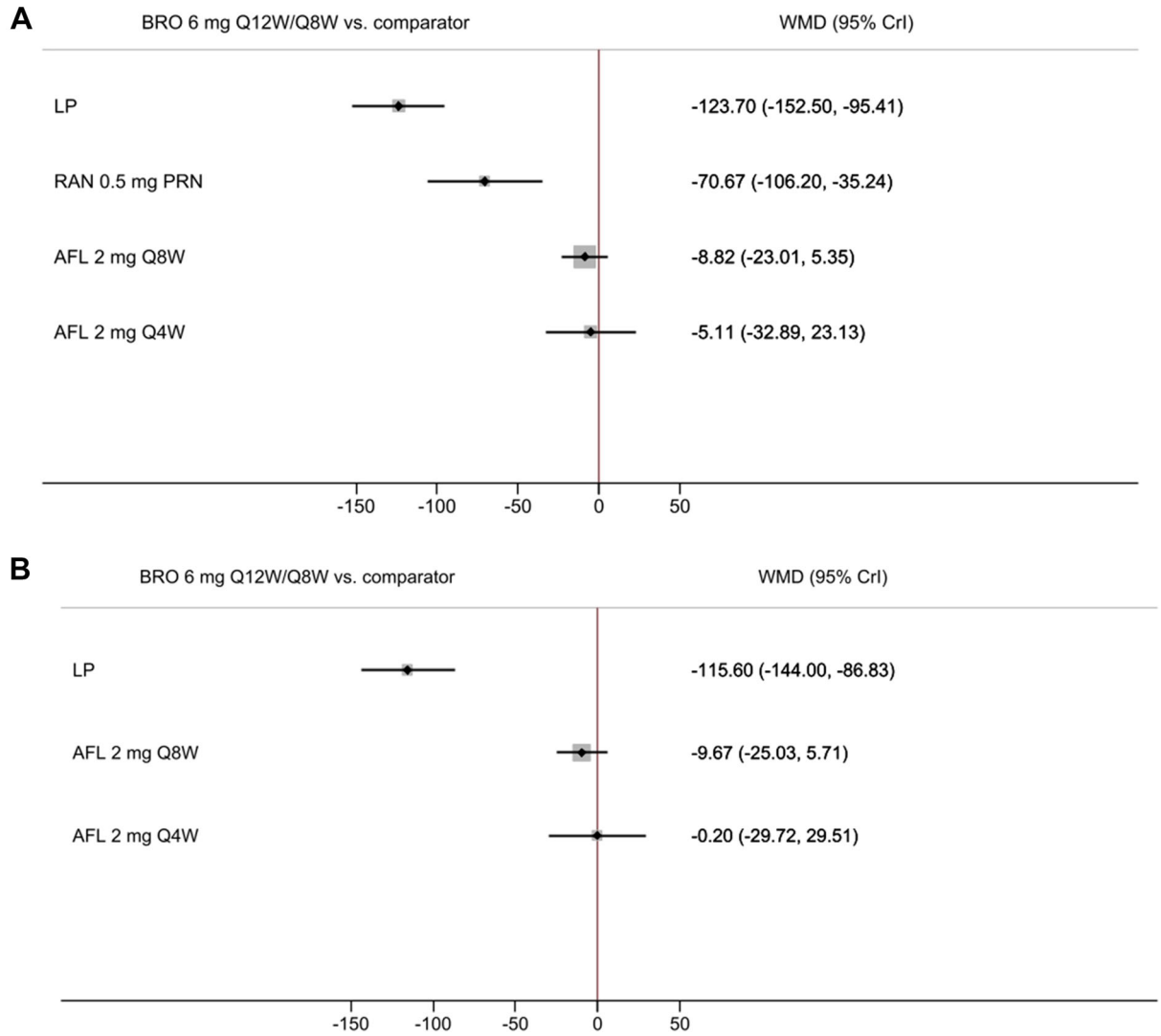

Fig. 4 Forest plot of the change from baseline in retinal thickness (μm) at **A** 1 year and **B** 2 years. Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; WMD, weighted mean difference

difference between aflibercept 2 mg PRN and ranibizumab 0.5 mg PRN.

The random effects model was preferred for this outcome. The anti-VEGFs were found to be mostly comparable; brolucizumab 6 mg was favoured over LP and ranibizumab 0.5 mg Q4W in gaining ETDRS letters over the course of 1 year of follow-up, with an increase of 10.22 (95% CrI 6.97, 13.68) and 5.41 (95% CrI 0.61, 10.47) letters from baseline, respectively (Table 2; Fig. 3). For studies with year 2 BCVA information, the change in visual acuity from baseline at year 1 was maintained until year 2 (Table 2).

For the year 1 analysis, some evidence of inconsistency between the direct and indirect evidence was observed ($p < 0.05$). However, it was not possible to identify one or more studies contributing to this inconsistency as two of three treatment paths in the single network loop were only informed by one study and the remaining path (ranibizumab 0.5 mg PRN vs LP) was informed by five studies demonstrating similar findings ($I^2 = 0\%$).

Table 4 All-cause study discontinuation and study discontinuation due to AEs, brolucizumab 6 mg Q12W/Q8W vs comparator

Intervention	Comparator	Study discontinuation (all-cause) Hazard ratio				Study discontinuation due to AEs Hazard ratio	
		No treatment pooling (fixed effects)		Treatment pooling (fixed effects)		No treatment pooling (fixed effects)	
		Median (95% CrI)	Mean (SD)	Median (95% CrI)	Mean (SD)	Median (95% CrI)	Mean (SD)
BRO 6 mg Q12W/Q8W	LP	1.21 (0.77, 1.92)	1.25 (0.3)	1.28 (0.83, 1.96)	1.31 (0.29)	0.68 (0.22, 2.04)	0.79 (0.48)
BRO 6 mg Q12W/Q8W	AFL 2 mg Q4W	1.08 (0.69, 1.71)	1.11 (0.26)	1.23 (0.87, 1.74)	1.25 (0.22)	0.76 (0.25, 2.28)	0.89 (0.54)
BRO 6 mg Q12W/Q8W	AFL 2 mg Q8W	1.23 (0.87, 1.74)	1.25 (0.22)			0.72 (0.27, 1.80)	0.80 (0.40)
BRO 6 mg Q12W/Q8W	AFL 2 mg PRN	1.86 (0.77, 5.04)	2.12 (1.14)			–	–
BRO 6 mg Q12W/Q8W	RAN 0.5 mg Q4W	***3.04 (1.29, 7.61)***	***3.41 (1.68)***	***2.03 (1.19, 3.47)***	***2.11 (0.59)***	1.47 (0.28, 8.43)	2.18 (2.46)
BRO 6 mg Q12W/Q8W	RAN 0.5 mg PRN	1.72 (0.96, 3.11)	1.8 (0.56)			0.89 (0.19, 3.93)	1.18 (1.03)

Font in bold and italics indicates one treatment is favoured over another
Abbreviations: AE, adverse event; AFL, aflibercept; BRO, brolucizumab; Crl, credible interval; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; SD, standard deviation

Proportion of Patients Experiencing BCVA Loss/Gain (Categorical Change)

Ten studies were included in the analysis of BCVA loss/gain at 1 year, and four studies were included in the analysis at 2 years (Table 1). Using the fixed effects model, brolucizumab 6 mg was found to be similar compared with the majority of anti-VEGF comparator regimens and favoured over LP and ranibizumab 0.5 mg Q4W at year 1, with relative effects estimated as *Z*-scores (*Z*-score −0.95 [95% CrI −1.16, −0.73] and −0.37 [95% CrI −0.70, −0.04], respectively) (Table 2). For treatments with year 2 data available, results on the probit scale also favoured brolucizumab 6 mg vs LP (*Z*-score −1.05 [95% CrI −1.29, −0.80]), with brolucizumab 6 mg similar to other anti-VEGF regimens (Table 2).

Diabetic Retinopathy Severity

Diabetic retinopathy can be categorised as a change in steps of severity, both in terms of improvement and progression. The most frequently reported severity category across studies was progression and improvement of ≥2 steps on the DRSS. Seven studies were included in the analysis of 2-step improvement from baseline in DRSS at 1 year, while the data set for 2 years follow-up only comprised four studies (Table 1).

Using the fixed effects model, at 1 year, brolucizumab 6 mg was favoured over LP (odds ratio [OR] 5.11 [95% CrI 3.14, 8.36]), and ranibizumab 0.5 mg PRN (OR 3.49 [95% CrI 1.26, 8.47]), and was similar to aflibercept 2 mg Q4W, and Q8W (Table 3). At 2 years, brolucizumab 6 mg was again favoured over LP in increasing the odds of experiencing a 2-step improvement

Table 5 Serious ocular and serious non-ocular AEs, brolucizumab 6 mg Q12W/Q8W vs comparator

Intervention	Comparator	Serious ocular AEs Hazard ratio				Serious non-ocular AEs Hazard ratio			
		No treatment pooling (fixed effects)		Treatment pooling (fixed effects)		No treatment pooling (fixed effects)		Treatment pooling (fixed effects)	
		Median (95% CrI)	Mean (SD)	Median (95% CrI)	Mean (SD)	Median (95% CrI)	Mean (SD)	Median (95% CrI)	Mean (SD)
BRO 6 mg Q12W/Q8W	LP	1.03 (0.36, 3.15)	1.21 (0.75)	1.25 (0.45, 3.56)	1.45 (0.83)	0.96 (0.66, 1.40)	0.97 (0.19)	0.97 (0.68, 1.37)	0.98 (0.18)
BRO 6 mg Q12W/Q8W	AFL 2 mg Q4W	1.04 (0.36, 3.14)	1.22 (0.74)	1.53 (0.62, 3.90)	1.72 (0.87)	0.85 (0.59, 1.24)	0.87 (0.17)	0.87 (0.67, 1.14)	0.88 (0.12)
BRO 6 mg Q12W/Q8W	AFL 2 mg Q8W	1.52 (0.62, 3.90)	1.71 (0.87)			0.87 (0.67, 1.14)	0.88 (0.12)		
BRO 6 mg Q12W/Q8W	AFL 2 mg PRN	4.56 (0.52, 146.8)	44.6 (1324)†			–	–		
BRO 6 mg Q12W/Q8W	RAN 0.5 mg Q4W	1.09 (0.02, 48.22)	11.06 (208.5)†	1.91 (0.38, 10.22)	2.75 (2.88)	1.31 (0.59, 2.98)	1.43 (0.62)	0.88 (0.53, 1.49)	0.92 (0.25)
BRO 6 mg Q12W/Q8W	RAN 0.5 mg PRN	1.75 (0.30, 11.12)	2.72 (3.45)			0.73 (0.40, 1.32)	0.76 (0.24)		

Abbreviations: AE, adverse event; AFL, aflibercept; BRO, brolucizumab; Crl, credible interval; LP, laser photocoagulation; PRN, pro re nata; QXW, every X weeks; RAN, ranibizumab; SD, standard deviation

†Median and 95% CrI are considered the most appropriate estimates, as SD values are unrealistic

in DRSS (OR 4.73 [95% CrI 2.81, 8.21]) and was similar to aflibercept 2 mg Q4W, and Q8W (comparison with ranibizumab was not possible).

Retinal Thickness

Eight studies were included in the analysis of change from baseline in retinal thickness at 1 year, while four studies were included in the analysis of change from baseline in retinal thickness at 2 years (Table 1).

Using the fixed effects model, brolucizumab 6 mg was favoured over both LP and ranibizumab 0.5 mg PRN at 1 year (Table 3; Fig. 4). The median estimated relative treatment effects were −123.7 µm (95% CrI −152.5, −95.41) and −70.67 µm (95% CrI −106.2, −35.24), respectively. At 2 years, the findings were similar, with brolucizumab 6 mg favoured over LP (relative mean difference −115.6 µm [95% CrI −144, −86.83]). No comparison with ranibizumab was possible. At both year 1 and year 2, brolucizumab 6 mg was similar

compared with aflibercept 2 mg Q4W and Q8W (Table 3; Fig. 4).

Safety and Tolerability Outcomes

Study Discontinuation (All-Cause)

An NMA was conducted for the reported study discontinuation rates, which included all-cause study discontinuation and treatment discontinuation rates. Twelve studies were included in the analysis of all-cause study discontinuation (Table 1).

Using the fixed effects model, discontinuation rates across treatments were similar, except for ranibizumab 0.5 mg Q4W, which showed fewer overall discontinuations when compared with all other treatments, including brolucizumab 6 mg (HR for brolucizumab 6 mg vs ranibizumab 0.5 mg Q4W 3.04 [95% CrI 1.29, 7.61]) (Table 4). Similar results were observed across pooled treatments, with brolucizumab, and pooled aflibercept regimens showing similar discontinuations, while ranibizumab showed fewer overall discontinuations compared with all other treatments (data not shown for all comparisons).

Study Discontinuation Due to Adverse Events

Nine studies were included in the analysis of study discontinuation due to AEs (Table 1). Using the fixed effects model, rates of discontinuation were similar across treatments (Table 4).

Serious Ocular Adverse Events

Ten studies were included in the analysis of serious ocular AEs as reported in the original pivotal trials (i.e. excluding IOI, RV, and RO) (Table 1). The low frequency of overall serious ocular AEs supports a favourable benefit/risk profile across all treatments, although this may result in unstable estimates of relative treatment effects. For both approaches (no pooling, pooled treatment regimens), using the fixed effects model, brolucizumab showed similar hazards of overall serious ocular AEs to all other treatment regimens or pooled treatment (Table 5). No treatment regimen or pooled treatment group showed favourable outcomes over any other (some CrIs were very wide with no pooling, even in the fixed effects model). Rates of adverse events of special interest (AESIs), including endophthalmitis, IOI, RV, and RO are reported in Table S15 in the supplementary material, with low rates of these events across trials. The rates of IOI, RV, and RO events were only reported in KESTREL and KITE, where brolucizumab 6 mg was associated with a higher rate of these events vs aflibercept 2 mg. Because of the heterogeneity in reporting these events and lack of reporting in other trials (Table S15), an NMA was not feasible.

Serious Non-Ocular Adverse Events

Seven studies were included in the analysis of serious non-ocular AEs (Table 1). Using the fixed effects model, all treatments were similar with respect to the frequency of serious non-ocular AEs, with no treatment favoured over the other.

DISCUSSION

The KESTREL and KITE trials provide randomised comparisons between brolucizumab 6 mg Q12W/Q8W and aflibercept 2 mg Q8W. However, with a number of anti-VEGF therapies recommended as first-line treatment in DMO, other comparisons with brolucizumab are also of interest and thus the objective of this NMA was to provide indirect comparisons for a number of doses and regimens of interest in country settings outside of the USA.

The NMA compared a number of visual and anatomical outcomes across treatments, improvements in which would have a meaningful impact for patients. BCVA is a measure of the best vision correction that can be achieved using glasses or contact lenses, and is vital for patient health-related quality of life (HRQoL); a 1-line (i.e. 5-letter) average change in BCVA has been associated with clinically meaningful changes in the visual functioning-questionnaire 25 (VFQ-25) [46]. We also compared DRSS score; patients who have a stable DRSS score, or who experience an improvement in DRSS have been shown to have greater mean changes in BCVA [47]. Retinal thickness is another characteristic

used to evaluate disease activity, progression, and treatment response. A build-up of fluid causes diffuse thickening of the macula, which may result in severely distorted central vision [2]. Given that the presence of fluid is a key criterion for determining injection intervals, a reduction in fluid assessed by central subfield/retinal thickness and no vision loss may indicate reduced disease activity and prolonged durability [11, 48–50]. For the anti-VEGF treatment doses and regimens considered in this NMA, efficacy benefits were similar for brolucizumab compared with aflibercept 2 mg and were either similar or favoured brolucizumab compared with ranibizumab 0.5 mg, while demonstrating a favourable benefit/risk profile.

In this NMA, brolucizumab had a similar change from baseline in central subfield thickness (CSFT) compared with aflibercept 2 mg Q4W and Q8W at year 1, and year 2. This conclusion differed from the individual head-to-head trial data available from KITE, in which brolucizumab demonstrated a superior change from baseline in CSFT versus aflibercept, due to the inclusion of data from KESTREL as well [31]. However, an NMA in the nAMD indication showed a significantly greater decrease in mean retinal thickness with brolucizumab compared with the comparators [51]. Real-world evidence studies could provide additional evidence of the benefit in anatomical outcomes for patients receiving brolucizumab for DMO in clinical practice.

This is the first analysis assessing the efficacy and safety of brolucizumab 6 mg for the treatment of patients with visual impairment due to DMO using a focused network based on the most relevant available comparators in non-US countries (aflibercept 2 mg, ranibizumab 0.5 mg). Studies included in the NMA were identified on the basis of an SLR to identify all relevant trials of interest and studies were mostly considered to be of high or medium quality, with only one rated as low quality (ReDes [44]) according to the JADAD scale. Of note, in KITE, there was a slight imbalance in baseline characteristics between study arms, in the mean baseline BCVA in the study eye and the proportion of patients presenting with ≤65 ETDRS letters at baseline [52]. However, slightly imbalanced baseline characteristics are not uncommon in pivotal studies, and although the mean baseline BCVA in the study eye was 2.3 letters higher in the brolucizumab arm (66.0 letters) vs the aflibercept arm (63.7 letters), this difference is not generally considered to be clinically significant, as evidenced by several clinical trials which use 3.5 to 5 letters as the margin to demonstrate a significant difference between drugs [31, 53–55]. Furthermore, the proportion of patients presenting with ≤65 letters at baseline was lower in the brolucizumab arm (36.3%) versus the aflibercept arm (50.3%) [52], and therefore inclusion of KITE data for brolucizumab in the NMA represents a conservative approach; generally, the higher the baseline BCVA, the smaller the number of letters gained because of the ceiling effect [56]. There was also limited information available on the number of patients receiving prior treatment across studies. For those studies reporting prior treatment status, high variability was observed, wherein patients across the studies were treated with different therapies. Only one study included a 100% treatment-naive population [45].

This analysis provides a synthesis of available evidence for several efficacy and safety outcomes at the time of a successful health technology assessment submission to NICE [26], and is representative of the different therapeutic regimens used in clinical practice. While the phase 3 trials KESTREL and KITE provided head-to-head evidence versus aflibercept, there is an absence of head-to-head phase 3 trial data for brolucizumab versus ranibizumab. Indirect treatment comparisons between brolucizumab and ranibizumab at different treatment regimens are provided by this study. The presented NMAs followed the generalised linear modelling framework recommended by the NICE DSU [38]. RCT evidence was systematically identified for inclusion in the NMA, with the quality of evidence mostly high with low risk of bias. Combining all relevant RCT evidence together in a single NMA analysis allowed new relative effect estimates to be calculated where treatments were not compared in head-to-head studies and enabled both direct and indirect evidence to contribute to the estimates.

The findings of this NMA are similar to the results of an NMA comparing brolucizumab 6 mg Q12W/Q8W with licensed anti-VEGF therapies, including aflibercept 2 mg and ranibizumab 0.5 mg regimens, for the treatment of patients with nAMD [51]. In this alternative indication, brolucizumab also demonstrated comparable gains in BCVA, discontinuation rates, and reduction in retinal thickness compared with these comparators at 1- and 2-years treatment.

The findings of the current NMA are limited by the small number of studies informing some treatment connections, even in the best case where all of the studies in the network reported outcome data. The sparsest data formed the comparison with the ranibizumab 0.5 mg Q4W node, which was only informed by one study, and the analyses were based on aggregate-level data and not individual patient data. In addition, the KESTREL and KITE trials had slightly different study designs, where patients receiving brolucizumab in KITE had the option to extend their treatment interval by 4 weeks (i.e. Q8W to Q12W, or Q12W to Q16W) if disease stability was observed at week 72 [36].

Injection frequency was an additional outcome of interest; however, it was not possible to generate robust estimates using this condensed network because of the small number of studies reporting mean injection frequency for either year 1 or year 2, combined with a sparse reporting of variance. Alternative methods for calculating injection frequency are reported by Sydnor et al. [57]. Notably, in the nAMD indication, brolucizumab showed superior reduction in retinal thickness, and comparable BCVA gains and discontinuation rates versus all licensed anti-VEGFs, while having the lowest annual injection frequency [51]. In an SLR of real-world evidence for brolucizumab in nAMD, all four studies identified investigating the injection interval after switching to brolucizumab from other anti-VEGFs observed extension of the treatment interval post switch [58].

Another limitation is the exclusion of other anatomical outcomes of interest in the KESTREL and KITE trials, such as the proportion of patients with subretinal fluid (SRF) and/or intraretinal fluid (IRF), as several trials in the network did not report this outcome. As a proxy, the change from baseline in central retinal thickness is a representation of the comparative efficacy of anti-VEGF therapies in anatomical outcomes.

After initial launch, a post-marketing safety signal of AEs RV and/or RO that may result in severe vision loss was identified with brolucizumab 6 mg [58–61]. In the HAWK and HARRIER trials, brolucizumab 6 mg was associated with higher rates of IOI-related AEs than aflibercept 2 mg [60]. Factors associated with increased incidence of these events include prior IOI and/or RO in the 12 months prior to brolucizumab treatment initiation, female gender, and Japanese ethnicity [62–64]. Additionally, brolucizumab must not be administered at intervals more frequent than Q8W after the initial loading phase because of increased risk of IOI-related AEs. These events were monitored in the phase 3 clinical trials, KESTREL and KITE, in the DMO indication [31]. In these trials, brolucizumab 6 mg was also associated with higher rates of IOI-related events vs aflibercept 2 mg. The rates of these events in KESTREL and KITE are in line with those in the HAWK and HARRIER (nAMD phase 3 trials), with the majority of the events being mild to moderate in severity and resolved without any sequelae [60]; no new safety signals were identified in the DMO indication, despite diabetes being a vascular and pro-inflammatory disease [31]. It should be noted that in a smaller real-world study of patients with nAMD, history of diabetes was suggested as a potential risk factor, but further research is needed in this area [65]. While these IOI-related events occur more frequently in the first 6 months after treatment initiation, they may also happen less frequently at a later stage [62, 66]. Therefore, patient education, and monitoring throughout treatment are advised. Prompt and aggressive treatment of inflammation plays a key role in mitigating and managing the impact of AEs related to IOI [67]. In fact, post-marketing reporting of rates of vision loss associated with RV and/or RO have shown a declining trend after an initial rise immediately after the identification of the safety signal [61], which may be related to the application of these

evidence-based recommendations. As the comparator studies included in the NMA did not report rates of IOI, RV, or RO events, it was not possible to perform baseline pooling or a description of these events for most trials included in the NMA, except for KESTREL and KITE. Therefore, the rates of these events are not reported for this NMA. AESIs also included endophthalmitis [31]; however, because of the heterogeneity in reporting these events, an NMA was not feasible.

CONCLUSION

This is the first study presenting a focused network based on the most relevant available comparators for brolucizumab in non-US countries for the treatment of patients with visual impairment due to DMO. The results demonstrated that brolucizumab 6 mg Q12W/Q8W was comparable or superior to other anti-VEGF regimens for key visual and anatomical outcomes including BCVA, diabetic retinopathy severity, and retinal thickness outcomes, while maintaining a favourable benefit–risk profile.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data sets analysed during the current study are available in the supplementary information. The code used during the current study is available from Novartis. Restrictions might apply to the availability of these data, which were used under licence for this study.

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