

Comparative Evaluation of Pegcetacoplan and Placebo on the Progression of Geographic Atrophy in Dry Age-related Macular Degeneration: A Systematic Review and Meta-analysis of Randomised Controlled Trials

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ABSTRACT

Introduction: As a late-stage dry Age-related Macular Degeneration (AMD), Geographic Atrophy (GA) historically, has had few effective therapeutic options, but pegcetacoplan (marketed as Syfovre) was recently approved by the Food and Drug Administration (FDA) for this indication in 2023. Pegcetacoplan inhibits C3 component of the complement system and reduces downstream inflammation and damage to the retina.

Aim: To examine the efficacy and safety of pegcetacoplan, a complement C3 inhibitor, in slowing GA progression by targeting complement dysregulation, compared with placebo.

Materials and Methods: The present systematic review and meta-analysis were performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered in International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024625783). A systematic search of MEDLINE, EMBASE, Scopus, Web of Science, ProQuest and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from inception to December 2024 was conducted. Randomised controlled trials (RCT) in English language evaluating intravitreal pegcetacoplan in GA secondary to dry AMD were included. Eligibility criteria for screening were RCTs of pegcetacoplan versus placebo/sham reporting efficacy {change in GA area and Best-Corrected Visual Acuity (BCVA)} and safety outcomes {Treatment-Emergent Adverse Events (TEAE), Serious Adverse Events (SAE), and Macular Neovascularisation (MNV)}. Data were extracted and risk of bias was assessed independently by two reviewers, using the RAYYAN tool and the Cochrane Risk of Bias 2 (RoB 2) Tool and any disagreement on study inclusion was resolved through discussion and consensus with a third author. We quantitatively

combined studies with similar participants, interventions, outcomes and methods using meta-analysis. Mean Differences (MDs) and Odds Ratios (OR) with 95% Confidence Intervals (CI) were computed using fixed and random-effects models in RStudio (v4.2.1) with the meta package, while heterogeneity was assessed using Cochran's Q (Chi-squared), Tau-squared and I² statistic.

Results: Seven eligible publications were included in the systematic review. Pegcetacoplan significantly slowed GA progression compared to placebo at 12 months (MD: -0.199; 95% CI: -0.372; -0.026; p=0.0236) and 24 months (MD: -0.760; 95% CI: -1.014; -0.507, p<0.001) respectively. No significant improvement in BCVA was observed at 12 and 24 months. Pegcetacoplan was associated with a 36% increase in TEAEs (OR: 1.36; 95% CI: 1.03; 1.81; p=0.03) and 53% increase in TEAEs (OR: 1.53; 95% CI: "1.04; 2.26"; p=0.03) at 12 months and 24 months respectively. No significant differences in SAEs at 12 months. Pegcetacoplan was associated with an approximately three-fold higher odds of MNV at 12 months (OR: 2.99; 95% CI: "1.12; 7.96"; p=0.029) and 24 months (OR: 3.17; 95% CI: "1.50; 6.73"; p=0.0026), respectively.

Conclusion: Pegcetacoplan considerably slows the progression of GA at 12 and 24 months in patients with dry AMD, but no significant improvement in visual acuity was observed. Treatment was associated with increased risk of TEAEs and MNV, but not SAEs, supporting a favourable but carefully balanced benefit-risk profile that merits further long-term evaluation. The magnitude and long-term durability of treatment effects should be interpreted with caution given the evidence available is based on a small number of underlying trial cohorts and further independent studies are warranted.

Keywords: Best-corrected visual acuity, Complement C3, Intravitreal injections, Macular neovascularisation, Treatment-emergent adverse events, Retinal degeneration

INTRODUCTION

Globally, an estimated 8.7% of individuals aged 45-85 years are affected by AMD. The increasing prevalence of AMD is becoming a major public health concern, with an estimated 288 million people being affected by AMD by the year 2040 [1]. AMD is broadly categorised into two forms-non exudative (or dry) and exudative

(or wet). GA accounts for approximately 20% of blindness due to advanced dry AMD [2]. GA is the result of progressive degeneration of the retinal pigment epithelium, photoreceptors, and choriocapillaris, resulting in irreversible vision loss and impaired activities of daily living [3]. Standard treatment of wet AMD involves anti-Vascular Endothelial Growth Factor (anti-VEGF) therapy

however there is no standard effective treatment in GA. As a result, there is ongoing investigation into strategies to prevent vision loss to GA. Dysregulation of complement system activation is one aspect that contributes to the pathogenesis of GA [4]. Although complement activation is vital component of tissue homeostasis and defending against pathogens, its overstimulation can cause retinal inflammation and destruction. Results from various genetic studies and histopathological studies have incriminated involvement of both C3 and C5 pathway in retinal degeneration [5].

Pegcetacoplan targets complement component C3, a central mediator of the complement cascade, thereby reducing downstream inflammation and retinal tissue damage associated with GA. Early clinical studies like FILLY trial first demonstrated its therapeutic potential by showing that complement inhibition can slow the progression of GA, providing a strong rationale for the subsequent development and evaluation of pegcetacoplan as a treatment for dry AMD [4,6,7]. The OAKS and DERBY trials confirmed this, further validating efficacy and safety in the phase III studies [8]. There is still an extension study underway that will provide more details on the long-term outcomes by late 2025 [9]. Although C5 inhibitors like avacincaptad pegol are effective, pegcetacoplan as a C3-targeted mechanism offers another target for complement inhibition, blocking inflammation prior to downstream activities involved later in the cascade [10]. This upstream action may boost the therapeutic effect, making pegcetacoplan a potential therapeutic option as an unmet need for GA.

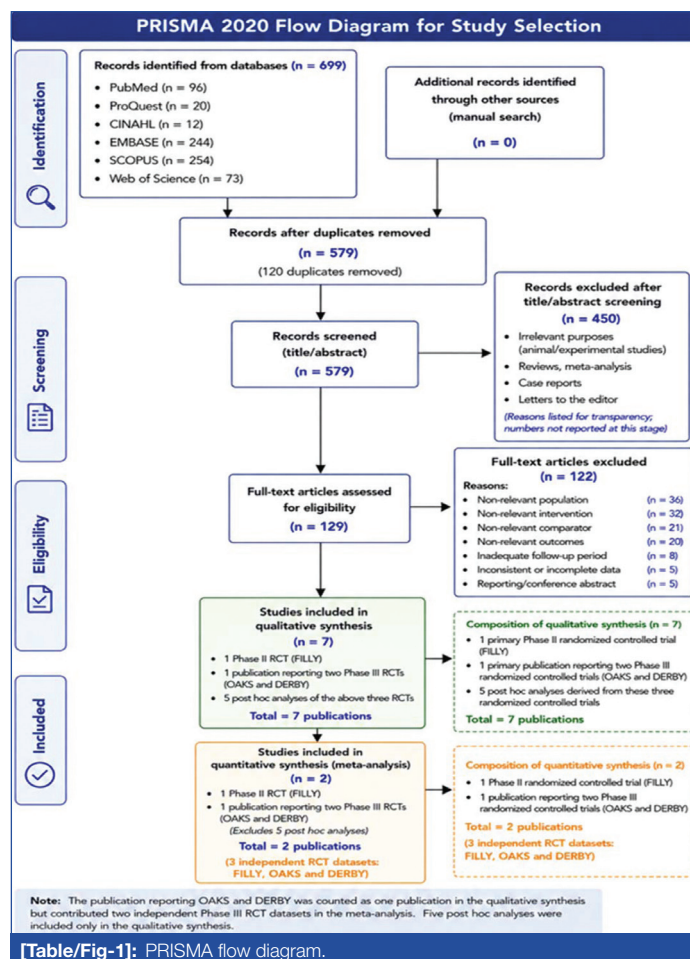
The primary objective of the present study was to evaluate the efficacy of pegcetacoplan in slowing the progression of GA compared with placebo at 12 and 24 months through a meta-analysis of RCTs. The secondary objectives were to compare changes in BCVA, TEAEs, SAEs, and MNV at 12 months, along with differences in BCVA at 24 months, between the pegcetacoplan and placebo groups. In order to improve knowledge of clinical efficacy of pegcetacoplan and its possible involvement in the management of GA, this review attempts to thoroughly synthesise the available data. This study underscores the importance of innovative treatments like pegcetacoplan to address the growing burden of AMD-related vision loss, in improving patient outcomes. This article presents a thorough up to date meta-analysis of RCTs that assessed the efficacy and safety of pegcetacoplan in delaying the progression of GA associated with dry AMD. To the best of authors' knowledge, the present study provides an updated synthesis and critical appraisal of phase II and phase III trial data on pegcetacoplan, incorporating recent publications available up to December 2024.

MATERIALS AND METHODS

The present comprehensive search was executed following the PRISMA reporting standards as shown in [Table/Fig-1] [11]. The protocol was registered preceding the start of the comprehensive search process. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number, ID: CRD42024625783. <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024625783>.

As depicted in [Table/Fig-1], the literature search turned up 699 documents from multiple electronic databases, and no more records were found by manual searching. After 120 duplicates were removed, 579 unique records underwent title and abstract screening, of which 450 were excluded. A total of 129 full-text articles were assessed for eligibility, and 122 were excluded for predefined reasons. Ultimately, seven publications were included in the qualitative synthesis, while two primary publications (representing three independent randomised clinical trial datasets) contributed to the quantitative synthesis (meta-analysis).

Inclusion criteria: The Problem/Patient/Population, Intervention/Indication, Comparison, and Outcomes (PICO) prototype was used to carry out this systematic review [12]. Studies were included if they met the following criteria:



[Table/Fig-1]: PRISMA flow diagram.

- Population:** RCTs including patients diagnosed with GA secondary to dry AMD.
- Intervention:** Pegcetacoplan administered via intravitreal injection (any dose or frequency).
- Comparison:** Placebo or sham control.
- Outcomes:** (i) Primary outcome: Change in GA area from baseline to 12 and 24 months.
(ii) Secondary outcomes: Change in BCVA, TEAEs, SAEs, and MNV.

Exclusion criteria: studies were excluded if they met any of the following criteria: i) non-RCT, observational studies, case reports or reviews; ii) studies involving patients with neovascular (wet) AMD or those previously treated with anti-VEGF therapy; iii) preclinical studies or animal studies; iv) studies with incomplete or insufficient data for meta-analysis; and v) studies published in language other than English.

Study Procedure

Data sources and search strategy: A thorough literature search was conducted across various electronic databases, such as MEDLINE (via PubMed), EMBASE, Scopus, Web of Science, ProQuest and CINAHL to identify all relevant RCTs written in English language from inception to December 2024 evaluating the efficacy and safety of pegcetacoplan in patients with GA secondary to dry AMD. Boolean operators (AND, OR) were used to refine the search. To execute our detailed research on these databases, we employed the following search strategy: ("age-related macular degeneration" OR "AMD" OR "geographic atrophy" OR "dry AMD" OR "non exudative AMD") AND ("pegcetacoplan" OR "APL-2" OR "Complement C3 inhibitors") AND ("RCTs" OR "RCT" OR "clinical trial"). In addition to database searches, we manually explored the reference lists of included articles to identify relevant articles. The detailed search strategy used for each database can be viewed in the supplementary material section.

Data were extracted independently by two reviewers using a standardised data extraction form. All disagreements about study selection and data extraction were resolved by discussion and, if necessary, by consulting a third reviewer until consensus was reached. Duplicate records were identified and removed using RAYYAN tool (<https://www.rayyan.ai/>). The remaining records were screened based on titles and abstracts, followed by full-text review. Extracted data included: study characteristics (author, year, study design, sample size), patient demographic (age, gender, race), intervention details (dose, frequency of administration), outcomes (changes in GA area, BCVA, TEAEs, SAEs, MNV).

Risk of bias assessment: For all included studies, we used the Cochrane RoB 2 tool for assessing the risk of bias methodology [13]. The Cochrane Handbook for Systematic Reviews of Interventions states that the following individual elements should be explicitly reported for RCTs: D1: Randomisation Process, D2: Deviations from Intended Interventions, D3: Missing Outcome Data, D4: Measurement of the Outcome, and D5: Selection of the Reported result. Each domain is assessed and colour-coded as red, yellow, green.

Data synthesis: The findings of the studies sufficiently similar in their participants, interventions, comparators, outcomes as well as methodology were pooled using quantitative meta-analysis. MDs with Standard Errors (SE) and 95% CIs were calculated for continuous outcomes between treatment groups. The results were illustrated through forest plots with individual and pooled effect estimates with 95% CIs. The studies reporting outcomes only at comparable time period were included in the analysis.

STATISTICAL ANALYSIS

Meta-analyses were performed using RStudio (version 4.2.1) with the meta-package (v8.0-1) following the Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024) [12]. The primary outcome was reduction in GA lesion area and change in BCVA was a secondary continuous outcome, both extracted as change in Least Square Mean (LSM) from baseline with SE. Safety and other secondary outcomes comprising of TEAEs, SAEs and MNV at 12 and 24 months were categorical and were extracted as number of events along with total patients in each arm for calculation of OR. Both arms were combined into a single pooled pegcetacoplan group prior to the meta-analysis, as Pegcetacoplan Monthly (PM) and Pegcetacoplan Every Other Month (PEOM) are the same active intervention. For continuous outcomes, arms were combined using sample-size-weighted mean averaging and variance propagation [12]. For binary outcomes, the number of events and total patients in the PM and PEOM arms were summed to form a single pooled pegcetacoplan group to estimate the OR versus sham. We preferred random-effects models to fixed-effect models because they provide more conservative estimates. MDs were pooled using Inverse-Variance and Restricted Maximum Likelihood (REML) methods and ORs were pooled using Der Simonian-Laird (random) and Mantel-Haenszel (fixed) methods. Heterogeneity was examined by forest plot overlap and Cochran's Q (chi-squared), Tau-squared and I^2 statistic, where I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively [14,15]. The leave-one-out sensitivity analyses across the three RCTs and pre-specified subgroup analyses according to pegcetacoplan dosing regimen (PM versus PEOM) were performed to assess the robustness of the results.

RESULTS

The total number of records identified through database searches was 699. Following the removal of 120 duplicate records, 579 records underwent titles and abstract screening. Finally, 129 full-text articles were assessed for eligibility in the study. Ultimately, seven studies met the inclusion criteria for qualitative synthesis as shown

in [Table/Fig-2,3] [4,8,16-20]. The included studies were by Liao DS et al., (2020), Heier JS et al., (OAKS & DERBY 2023), Steinle NC et al., (2021), Vogl WD et al., (2023), Fu DJ et al., (April 2023, September 2023, 2024). Two RCTs, OAKS and DERBY, included under the Heier JS et al., were analysed separately [4,8,16,17].

The seven included studies comprised published data from the Phase II FILLY trial {Liao DS et al., (2020)}, four post-hoc analyses of the FILLY trial, one manuscript presenting separate data from the Phase III OAKS and DERBY trials (Heier JS et al.), and one post-hoc analysis of the same Phase III trials. Details of the dosing and frequency of intravitreal pegcetacoplan administration, sample size, demographics including age, gender, race, follow-up duration, as well as primary and secondary outcomes are summarised in [Table/Fig-3] [4,8,16-20]. The Sample size across the studies ranged from 144 to 936 participants, taking into account the population diversity, with follow-up periods of 52-104 weeks. The mean age across studies was 77.2-79.5 years, about 60% were female, and over 78% were White, reflecting limited racial diversity as shown in [Table/Fig-2] [4,8,16-20].

Risk of bias assessment: The Cochrane RoB 2 tool was used to evaluate the methodological quality of the studies included in the current review as shown in [Table/Fig-4] [4,8,16-20]. A very strong methodological rigour was demonstrated by the low risk of bias (as shown in green colour) across all domains. Minor concerns related to missing outcome data (D3) were noted in Steinle NC et al., Vogl WD et al., and Fu DJ et al., shown in yellow [16-18]. Studies such as Liao DS et al., (2020), Heier JS et al., and Fu DJ et al., demonstrated consistently low bias [4,8,19]. RoB 2 assessment as illustrated in [Table/Fig-4] was done to check overall validity and reliability assessment of the pooled results [4,8,16-20].

Extracted data from studies: The efficacy of Pegcetacoplan in treating GA caused by dry AMD was evaluated and summarised as shown in [Table/Fig-3]. Pegcetacoplan (every month) consistently slowed GA progression compared to placebo. For example Fu DJ et al., reported a GA increase of 0.151 ± 0.142 mm², while Fu DJ et al., showed changes between 0.79 (PM)- 1.14 (Sham) mm² at 12 months [18,19]. Liao DS et al., demonstrated significant changes in GA area in LSM (0.26 ± 0.025 mm²) at 12 months in PM [4]. Heier JS OAKS and Heier JS DERBY reported GA area changes in LSM of 1.5579 and 1.7344 mm², respectively at 12 months in PM [8]. A similar reduction was observed in the PEOM group as well. Despite structural benefits, BCVA changes in LSM were modest at 12 months, ranging from -2.575 to -3.31 letters in PM group across the studies. The studies confirm the efficacy of Pegcetacoplan in slowing GA progression, though functional visual improvements remained limited over 12 months. Heier JS OAKS and Heier JS DERBY reported GA area changes in LSM of 3.1237 and 3.2275 mm², respectively at 24 months in PM. A similar reduction was observed in the PEOM group as well [8].

Primary outcome: change in Geographic Atrophy (GA) area: The primary outcome of interest was the change in GA area from baseline to 12 months and 24 months. This metric, derived from fundus imaging, offers a standardised measure of GA progression. The changes in GA area at 12 and 24 months were illustrated in forest plot of [Table/Fig-5] [4,8]. All included studies showed a consistent reduction in GA area progression. Meta-analysis of the included trials demonstrated that pegcetacoplan significantly slowed the progression of GA compared to placebo at 12 months as shown in [Table/Fig-5a], where the random effect model MD (MD: -0.199; 95% CI: "-0.372; -0.026"; $p=0.0236$). Nevertheless, significant between-study heterogeneity ($I^2=75.6\%$) was connected with this analysis, suggesting significant variation in the size of treatment effects among these included studies. The pooled data from two studies illustrated in [Table/Fig-5b], showed statistically significant change in GA area reduction at 24 months (MD: -0.760; 95% CI: "-1.014; -0.507"; $p<0.001$).

S. No.	Author, year	Agent, dose, action	Type, design	No of patients in each study arm (n)	Age (years) (Mean±SD)	Gender (female) (n, %)	Race (White) (n, %)	Follow-up	Primary outcome
1	Liao DS et al., (2020)[4]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	FILLY trial, phase II, RCT	246 (86 PM;79 PEOM;81 SM)	79.6±7.5; 80.9±7.5; 78.4±7.4	55(64.0); 50(63.3); 49(60.5)	84(97.7); 76(96.2); 81(100.0)	78w	Least square root mean & Square root of the change in the GA area
2	Steinle NC et al., (2021) [16]	Intravitreal Pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	post hoc, FILLY trial	192 (67 PM; 58 PEOM;67SM)	NA	44(66), 37(64), 67(74)	NA	52w	Risk factors for GA progression
3	Vogl WD et al., (2023)[17]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	post-hoc, FILLY trial	156 (PM 57; PEOM 46; SM 53)	79.5±7.7 79.5±7.6 77.1±7.4	37(64.9) 28(60.9) 35(66.0)	NA	78W	LPR of GA, PR thickness, and HRF concentration in mm.
4	Fu DJ et al., (April 2023) [18]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	post hoc, FILLY trial	197 (71 PM; PEOM 61; SM 65)	80.4±7.44 80.3±7.43 77.9±7.58	45(63.4) 40(65.6) 39(60)	NA	52 weeks treatment, 26 weeks monitoring	Reduced CRORA growth: PM vs Sham: 45% reduction, PEOM vs Sham: 27%
5	Heier JS et al., (2023)[8]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	OAKS Phase III trial	614(202 PM; 205 PEOM; 207 SM)	78.8±7.2 78.1±7.77 78.6±7.3	125(62%) 117(57%) 133(64%)	185(92%) 189(92%) 188(91%)	104w	Change in mean GA area
	Heier JS et al., (2023)[8]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	DERBY Phase III trial	597(201 PM; 201 PEOM; 195 SM)	78.7±6.9 79.2±7.1 78.6±7.3	118(59%) 120(60%) 123(63%)	187(93%) 186(93%) 188 (96%)	104w	Change in mean GA area
6	Fu DJ et al., Sept (2023) [19]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	post hoc, FILLY trial	144 (48 PM; PEOM 46; SM 50)	80.7±7.22 79.9±7.87 77.8±7.36	32(66.7) 29(63.0%) 30(60.0%)	46 (95.8%) 43 (93.5%) 49 (98.0%)	52W	Slowed GA growth (RORA, PRD, RPE-loss, intact macula)
7	Fu DJ et al., (2024)[20]	Intravitreal pegcetacoplan (APL-2) 15 mg (0.1 mL), C3 inhibitor	post hoc for OAKS/DERBY studies	936 (310 PM; PEOM 309; SM 317)	78.5±7 78.7±7.58 78.4±7.11	189(61.0) 177(57.3) 204(64.4)	284(91.6) 283(91.6) 295(93.1)	104w	Change in GA area, PRD, RPE loss, RORA

[Table/Fig-2]: Characteristics Summary of included studies in Systematic review and meta-analysis [4,8,16-20].

W: weeks; PM: Pegcetacoplan every month; PEOM: Pegcetacoplan every other month; SM: Sham; CRORA: Complete RPE and Outer Retinal Atrophy; RORA: RPE and outer retinal atrophy; RPE: Retinal pigment epithelium; PRD: Photoreceptor degeneration; LPR: Loss of the photoreceptor layer; PR: Photoreceptor; HRF: Hyperreflective foci

Important footnote: The analysis included seven publications, but the study by Heier JS et al., included two independent Phase III RCTs (OAKS and DERBY) and these were analysed separately.

S. No.	Study, year	Change in square root GA area at 12 months (Mean±SD, mm²)	Change in GA area in mm² at 12 months (LSM, SE)	Change in GA area in mm² at 24 months (LSM, SE)	Change in BCVA at 12 months (LSM±SE) (Letters)	Change in BCVA at 24 months (LSM±SE) (Letters)	TEAE at 12 months	SAE at 12 months
1	Liao DS et al., (2020) [4]	0.252±0.113 (Weighted n=64); 0.276±0.111 (Weighted n=60); 0.345±0.126(Weighted n=67)	0.26±0.025 (n=84) 0.28±0.026 (n=78) 0.35±0.025 (n=80)*	NA	-3.31±1.352(N=84); -5.78±1.398(N=78); -5.8±1.1(N=80)	NA	65, 49, 47	4, 2, 1
2	Steinle NC et al., (2021) [16]	0.26±0.17, 0.27±0.26, 0.36±0.21	NA	NA	NA	NA	NA	NA
3	Vogl WD et al., (2023) [17]	1.1±0.405 1.133±0.701 1.174±0.788	NA	NA	NA	NA	NA	NA
4	Fu DJ et al., (April 2023) [18]	0.151±0.142 (n=56) 0.202±0.256(n=52) 0.277±0.209(n=58)	NA	NA	NA	NA	NA	NA
5	Heier JS et al., (OAKS) (2023) [8]	NA	1.5579±0.0835 (n=202) 1.6512±0.0812 (n=204) 1.9692±0.0822 (n=205)	3.1237±0.14327 (n=202), 3.2826±0.13238 (n=204), 4.0252±0.14642 (n=206)	-2.575±0.376 (n=403); -3.725±0.553 (n=406); -2.5±0.540 (n=402)**	-7.477±1.052, -8.526±1.052, -7.660±1.073	171, 161, 155	5, 4, 1
	Heier JS et al., (DERBY) (2023) [8]	NA	1.7344±0.0792 (n=200) 1.7563±0.0744 (n=199) 1.9640±0.0959 (n=193)	3.2275±0.12457 (n=200), 3.3395±0.13034 (n=200), 3.9726±0.16820 (n=194)		-8.126±1.018, -8.947±1.032, -6.217±1.017	159, 157, 145	4, 2, 2
6	Fu DJ et al., Sept (2023) [19]	0.796±0.409 (n=56) 0.849±0.684 (n=52) 1.147±0.473 (n=58)	NA	NA	NA	NA	NA	NA
7	Fu DJ et al., (2024) [20]	NA	1.18±0.07 (N=298) 1.42±0.06 (N=299) 1.79±0.08(N=307)	NA	-3.02±0.55 (N=298); -4.51±0.64(N=299); -2.75±0.64(N=307)	NA	NA	NA

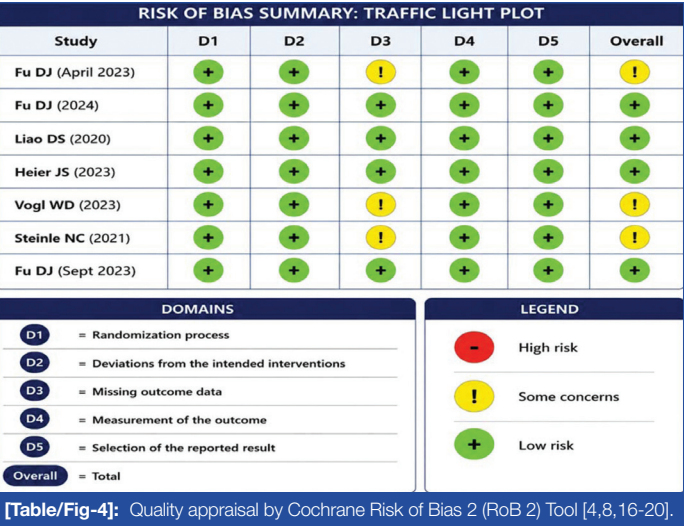
[Table/Fig-3]: Extracted data from studies included in the systematic review and meta-analysis [4,8,16-20].

*Note: In Liao DS et al., (2020), 246 participants were included in the demographic analysis, while 242 participants were included in the final GA area analysis. **Note: BCVA data at 12 month were derived from the combined OAKS/DERBY analysis reported by Heier JS et al., Abbreviations: NA: Not available; SD: Standard deviation, LSM: Least square mean, SE: Standard error

Secondary outcome: The forest plots depicting the changes in BCVA at 12 months and 24 months for each study are displayed in [Table/Fig-6] [4,8]. In the pooled three-study analysis of BCVA at 12 months [Table/Fig-6a], there was no statistically significant difference between groups (MD: -0.124; 95% CI: “-1.824; 1.577”; p=0.886), and low heterogeneity was detected ($I^2=32.9\%$). This CI is very wide and contains potentially meaningful harm and benefit, which is consistent with considerable imprecision from the small number of studies. So, the 12-month BCVA result has to be deemed

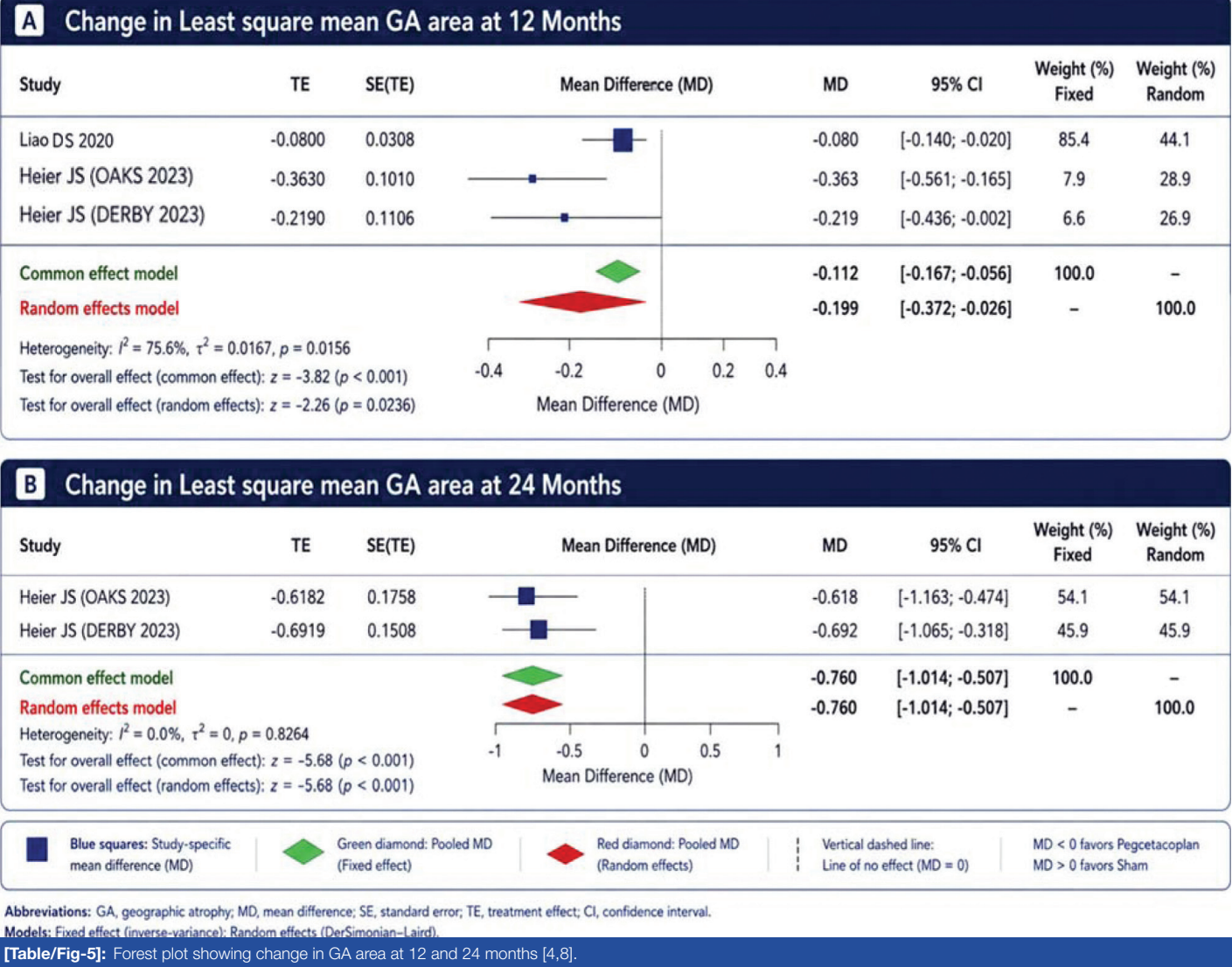
highly uncertain and inconclusive. Pooled data from two studies at 24 months demonstrated no statistically significant difference in BCVA (MD: 1.379; 95% CI: “-0.389; 3.146”; p=0.126), and no heterogeneity was detected ($I^2=0\%$) [Table/Fig-6b]. This estimate is based on just two studies and should also be considered tentative and uncertain.

The safety outcomes were illustrated as forest plot in [Table/Fig-7,8] at 12 months and 24 months, respectively [4,8]. At 12 months, pegcetacoplan was associated with significantly increased odds



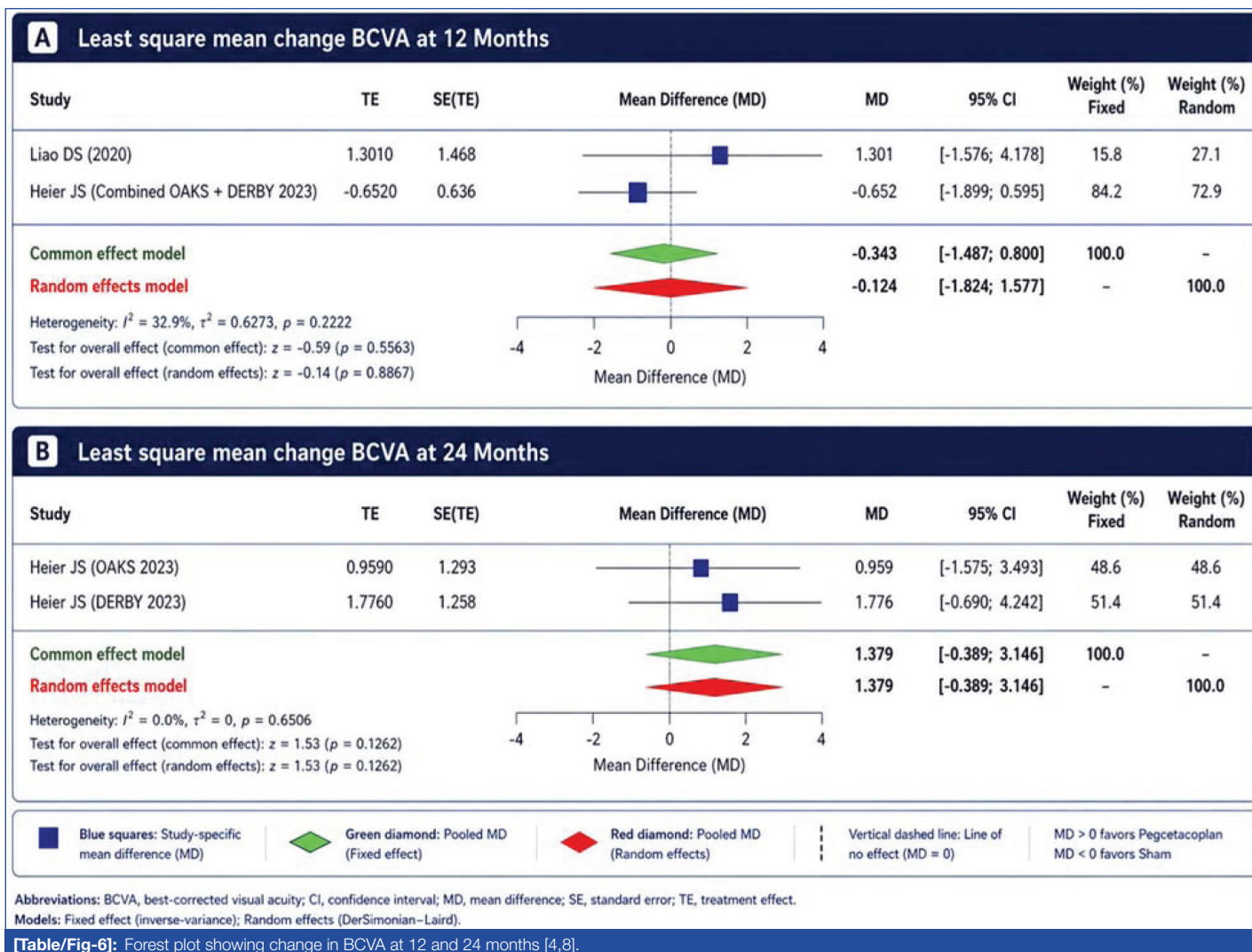
was no heterogeneity among the studies ($I^2=0\%$). Pegcetacoplan was associated with a significantly increased risk of MNV compared with sham (OR: 3.17; 95% CI: "1.50; 6.73"; $p=0.0026$) as depicted in [Table/Fig-8b]. There was low heterogeneity ($I^2=22.4\%$) suggesting a similar three times higher risk across studies. Pegcetacoplan did not show any statistically significant improvement in monocular reading speed or functional reading independence at 24 months versus sham as shown in [Table/Fig-9a,b] in supplementary material. Pooled estimates were non-significant under fixed and random-effects models. No heterogeneity was observed between studies ($I^2=0\%$).

Statistical Heterogeneity and Methodological Consistency: Heterogeneity was assessed using the Chi-squared test, Tau-squared (τ^2), I^2 statistic and visual inspection of forest plots [Table/Fig-5-8]. For the GA area [Table/Fig-5], significant heterogeneity was observed at 12 months ($I^2=75.6\%$), but no heterogeneity at 24 months ($I^2=0\%$), suggesting consistent treatment effects over longer follow-up. BCVA outcomes [Table/Fig-6] displayed low-



of TEAEs compared to sham (OR: 1.36; 95% CI: "1.03; 1.81"; $p=0.03$) with low heterogeneity, indicating 36% increased odds as depicted in [Table/Fig-7a]. Though incidence of SAEs were more in pegcetacoplan group, still there were no statistically significant differences between groups for SAEs (OR: 2.60; 95% CI: "0.80; 8.48"; $p=0.11$) as shown in [Table/Fig-7b]. Pegcetacoplan treatment was significantly associated with an increased risk of MNV compared with sham, with a pooled random-effects OR of 2.99 (95% CI: "1.12; 7.96"; $p=0.029$) with moderate heterogeneity ($I^2=37.1\%$) as depicted in [Table/Fig-7c]. Pegcetacoplan was associated with a significantly higher incidence of TEAEs than sham at 24 months (OR: 1.53; 95% CI: "1.04; 2.26"; $p=0.03$) as shown in [Table/Fig-8a]. There

to-moderate heterogeneity at 12 months ($I^2=32.9\%$) and no heterogeneity at 24 months ($I^2=0\%$). Safety outcomes showed little variability between studies. TEAEs [Table/Fig-7] and SAEs, [Table/Fig-7] demonstrated negligible heterogeneity ($I^2=0\%$), whereas MNV, [Table/Fig-8] demonstrated low-moderate heterogeneity at 12 months ($I^2=37.1\%$) and low heterogeneity at 24 months ($I^2=22.4\%$). Visual inspection of [Table/Fig-5-8], revealed a consistent direction of effect with overlapping CIs for most outcomes, indicating trial comparability and appropriateness of pooling data using fixed or random-effects models as appropriate. We conducted leave-one-out sensitivity analyses to test the robustness of the effect of pegcetacoplan on GA area progression



at months 12 and 24 as shown in [Table/Fig-10a,b] [4,8]. All pooled MDs at 12 months were negative and consistently favoured pegcetacoplan. Exclusion of Liao DS et al., increased the treatment effect and exclusion of either the OAKS or DERBY trial decreased statistical significance but the direction and magnitude of the effect was generally maintained with minimal heterogeneity ($I^2 < 1\%$). At 24 months, exclusion of either OAKS or DERBY did not change the direction of effect and both individual trials continued to show a significant benefit of pegcetacoplan versus sham. Although interpretation is hampered by the small number of studies available, these findings support the consistency of the observed treatment effect across analyses.

Pegcetacoplan significantly slowed GA area growth compared with sham at 12 and 24 months. Treatment effect was observed for both monthly (PM) and every-other-month (PEOM) regimens. Subgroup analyses showed no significant differences between dosing PM and PEOM regimens (test for subgroup differences: $p = 0.688$ at 12 months and $p = 0.518$ at 24 months), suggesting similar efficacy of both as depicted in [Table/Fig-11a,b] in supplementary section. PM showed numerically greater reductions in GA progression as compared to PEOM, but none of the differences reached statistical significance. The benefit was larger at 24 months than at 12 months, suggesting a sustained treatment effect over time. With comparable efficacy for both regimens, PEOM could be a more feasible and cost-effective alternative to the reduction in the number of invasive intravitreal injections, clinic visits, treatment burden and associated healthcare costs.

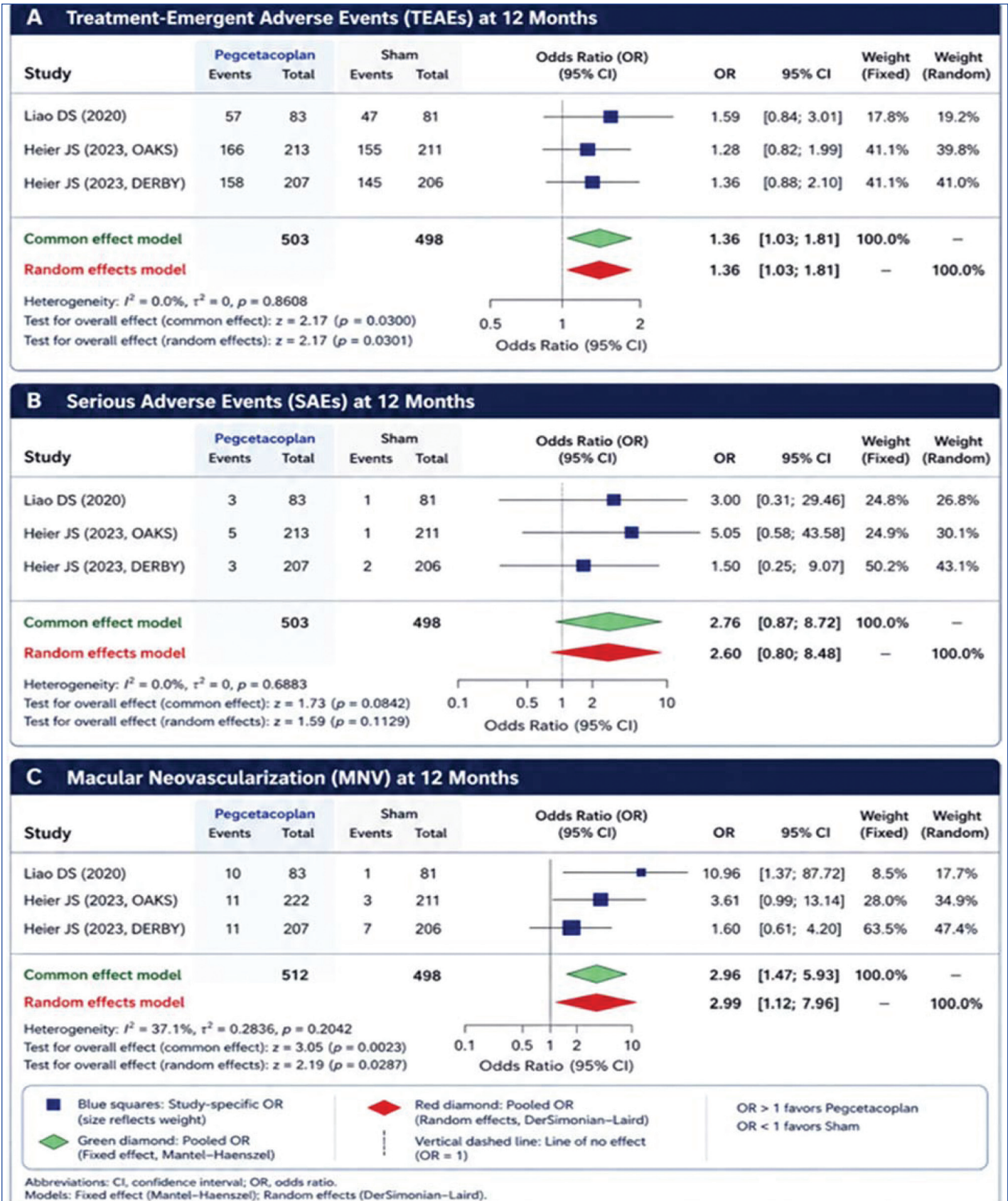
DISCUSSION

The current systematic review and meta-analysis suggest that, in patients with dry AMD, pegcetacoplan effectively slows the GA

progression. Evidence from included RCTs and post hoc analyses indicated that pegcetacoplan significantly reduced GA lesion growth compared with sham controls. This finding is clinically important, given the limited treatment options for GA and its major contribution to vision loss in older adults. However, no meaningful improvement in BCVA was observed at either 12 or 24 months.

Pegcetacoplan is a pegylated peptide that inhibits complement components C3 and C3b. Complement dysregulation is a critical mechanism in GA pathogenesis, with excessive complement activation driving inflammation, immune-mediated injury, and apoptosis of the retinal pigment epithelium and photoreceptors [4]. The continued decrease in GA area across the studies is consistent with complement control as an important mechanism, and previous evidence has shown that GA enlargement is associated with worsening visual function such as decreased BCVA and contrast sensitivity [2], so slowing GA growth could be important in maintaining useful vision and quality of life.

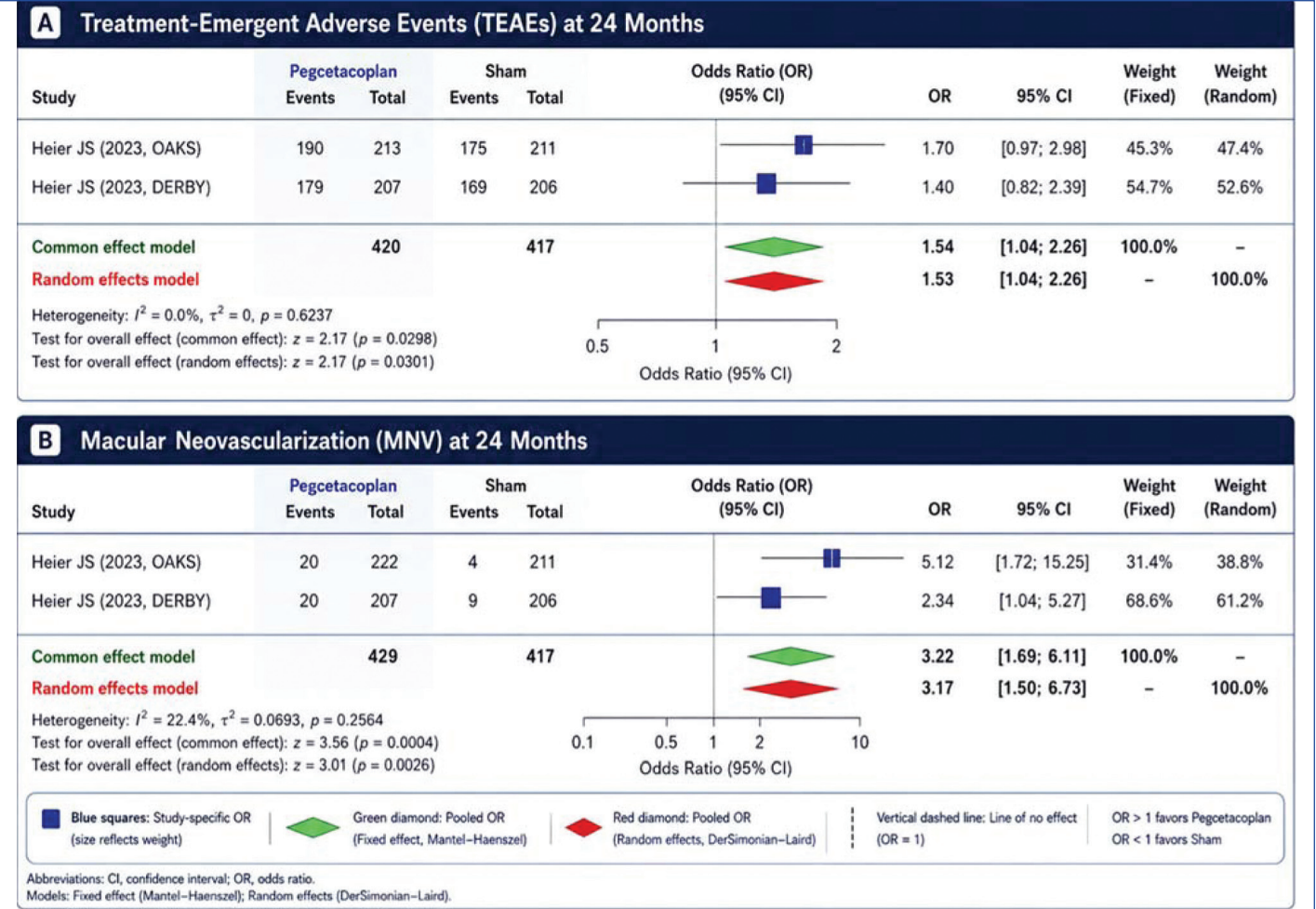
The primary outcome was the change in GA area in LSM from baseline to 12 and 24 months. These transformations address the non-linear growth of GA and minimise variability across studies. The LSM change from baseline in the square root-transformed GA lesion area at 12 months was the main effectiveness outcome. Because it reduces the dependence of lesion growth rates and test-retest variability on baseline lesion size, square root transformation is the standard analytical method in GA clinical trials. This results in a more reliable and comparable evaluation of disease progression across treatment groups [21]. This meta-analysis revealed that pegcetacoplan led to a significantly slower progression of GA compared with sham control. The forest plot demonstrated a statistically significant



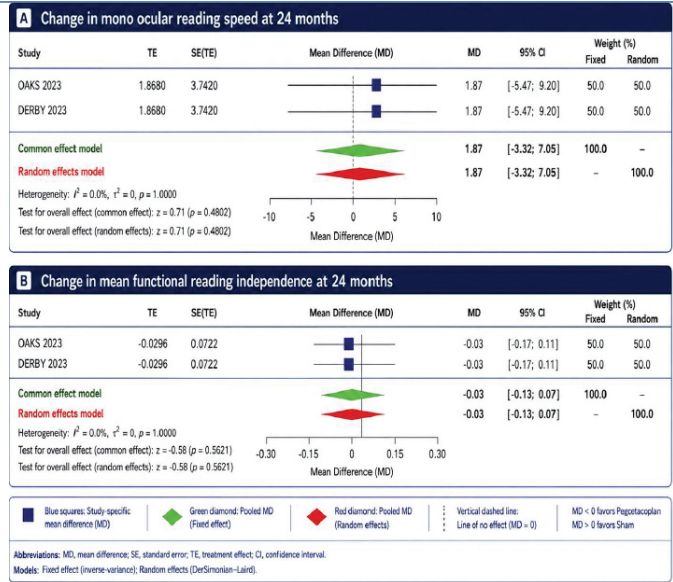
[Table/Fig-7]: Forest plot showing Odds Ratio (OR) for assessment of safety at 12 months [4,8].

reduction in the LSM change in GA lesion area at 12 months (MD: -0.199; 95% CI: "-0.372 to -0.026"), with the CI excluding the null effect and substantial heterogeneity among studies ($I^2=75.6\%$), which should be interpreted cautiously. In the current review, patients treated with pegcetacoplan demonstrated a significant change in GA area within a 24-month timeframe (MD: -0.760; 95% CI: "-1.014; -0.507"). While decreased GA size is an important structural change, it does not always result in immediate, direct improvements in vision; however, GA lesion size is highly related to visual function, and therefore size changes are

considered clinically relevant. Another novel drug avacincaptad pegol (a complement C5 inhibitor) demonstrated statistically significant dose-dependent reductions in GA progression similar to pegcetacoplan, with treatment effects approaching > 25% versus sham therapy as C5 inhibition theoretically preserves C3 activity [10,22]. However, while eculizumab (a systemic inhibitor of complement component C5) and lampalizumab (an inhibitor of the alternative complement pathway directed against complement factor D) demonstrated biological activity in eyes with GA, these effects did not translate into a significant reduction in GA lesion



[Table/Fig-8]: Forest plot showing Odds Ratio (OR) for assessment of safety at 24 months [8].



[Table/Fig-9]: Forest plots showing the effect of pegcetacoplan versus sham on monocular reading speed (A) and mean functional reading independence (B) at 24 months.

improvements at either the 12- or 24-month assessment period, which is also in correspondence to a 2-year pegcetacoplan study reported by Apellis Pharmaceuticals as well as similar observations reported with lampalizumab and avacincaptad pegol therapies [25,26]. This disconnection suggests the need for different targets, combination therapies and sensitive endpoints for GA. Pegcetacoplan significantly slows GA growth with similar efficacy for PM and PEOM dosing, supporting PEOM as a cost-effective option, decreasing injection burden while maintaining benefit.

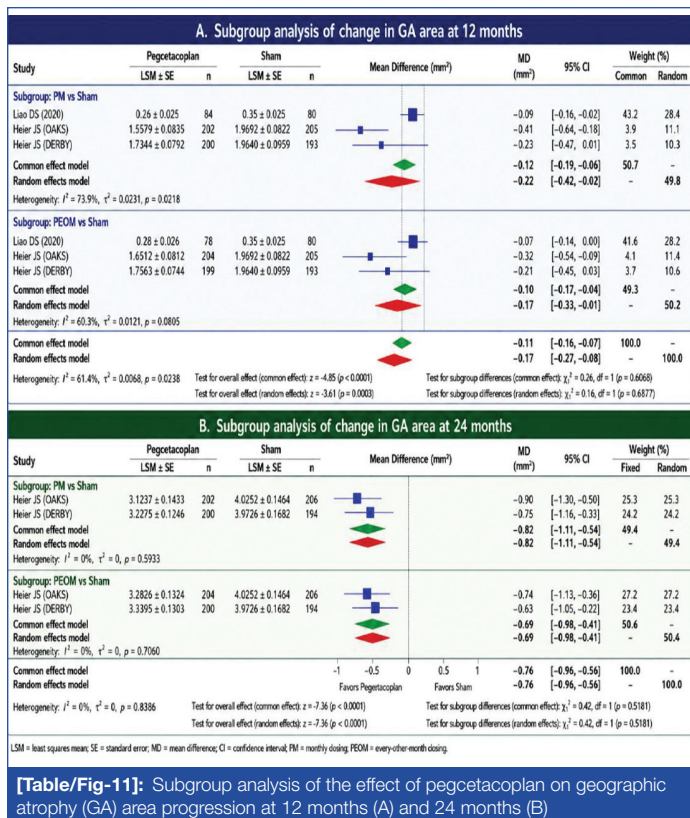
A safety comparison across all of the studies showed that pegcetacoplan had a statistically significant higher risk of TEAEs and MNVs at 12 and 24 months, whereas there were no significant differences between pegcetacoplan and placebo for SAEs. There was no difference between pegcetacoplan and sham in visual acuity; however, pegcetacoplan caused more adverse events than sham, which indicates that close monitoring of treatment safety during use of pegcetacoplan is warranted.

The studies included were meticulously designed with low-risk of bias across the key domains. This strengthened confidence in the pooled estimates. The potential biases were considered and addressed by the Cochrane RoB 2 quality assessment tool [13]. The I^2 statistic, Chi-squared test, and forest plot interpretation used to assess, which showed low to moderate heterogeneity

growth [23-25]. Pegcetacoplan was not associated with BCVA

a. Leave-one-out sensitivity analysis for change in GA area at 12 months				b. Leave-one-out sensitivity analysis for change in GA area at 24 months			
Omitted Study	MD (95% CI)	p-value	I ² (%)	Omitted Study	MD (95% CI)	p-value	I ² (%)
None	-0.199 (-0.372, -0.026)	0.024	75.6	None (all studies)	-0.760 (-1.014, -0.507)	<0.001	0
Liao DS et al., 2020	-0.298 (-0.444, -0.151)	<0.001	0	Heier JS (OAKS 2023)	-0.689 (-1.103, -0.275)	0.001	NA*
OAKS 2023	-0.109 (-0.219, 0.002)	0.054	0.3	Heier JS (DERBY 2023)	-0.822 (-1.216, -0.427)	<0.001	NA*
DERBY 2023	-0.205 (-0.481, 0.070)	0.144	0.9				*I ² could not be calculated because only a single study remained after exclusion.

[Table/Fig-10]: Leave-one-out sensitivity analyses for change in Geographic Atrophy (GA) area progression at 12 months (a) and 24 months (b) [4,8].



[Table/Fig-11]: Subgroup analysis of the effect of pegcetacoplan on geographic atrophy (GA) area progression at 12 months (A) and 24 months (B)

[14]. This supported consistency of the effects of pegcetacoplan across trials. A random-effects model was applied which appropriately accounted for within-study and between-study variability [15].

This meta-analysis suggests that pegcetacoplan slows progression of GA lesions but does not preserve vision at 12 or 24 months, highlighting a disconnect between structural and functional outcomes. Early reduction in expansion of lesions may impact upon long-term vision. The importance of early treatment may need further delineation [16]. Therapies like pegcetacoplan have been developed to treat GA and have consistently slowed lesion progression, though safety concerns such as neovascular complications persist. Non-pharmacologic approaches, such as photo biomodulation and dietary supplementation or targeting other noncomplementary pathways, may provide more modest benefit, particularly in early-stage disease. Longer-term, larger studies are needed to confirm the safety, efficacy and best ways to treat these emerging therapies [27].

Future studies should focus on evaluating long-term outcomes on pegcetacoplan assessing the long-term functional impact as well as quality of life of patients with GA with dry AMD. Add on neuroprotective and/or anti-inflammatory agents with pegcetacoplan may provide better clinical outcome. Besides, research should focus on the biomarkers, which allow personalised management.

Previous GA trials have negative/neutral outcomes: eculizumab (systemic C5 inhibitor) showed no significant GA growth reduction and emixustat (visual cycle modulator) did not reduce GA compared to placebo with visual side effects. Fenretinide showed only trend-level effects without statistical significance. Brimonidine (neuroprotection) and ciliary neurotrophic factor (CNTF) implant had good safety, mixed/subset signals in lesion growth or visual acuity preservation but were not approved [28]. These completed negative trials contrast with approved complement inhibitors achieving GA reduction without BCVA benefit and highlight challenges of GA treatment. In advanced Phase III trials for GA, vonaprunten (C1q inhibitor), tinlarebant (oral vitamin A reducer), elamipretide (mitochondria-targeting peptide), cemdisiran (C5 inhibitor), and iptacopan (oral Factor B inhibitor) are ongoing, awaiting results [28].

Limitation(s)

Several limitations should be considered when interpreting the findings of this review. Subgroup analyses by dosing regimen (monthly vs. every other month) and leave-one-out sensitivity analyses were performed and generally supported consistency of results, but were limited by the small number of available randomised controlled studies. The sensitivity analyses are limited in the extent to which conclusions can be drawn, especially in the case of some 24-month outcomes where exclusion of one study resulted in a single-study estimate rather than a truly pooled effect. Additionally, the majority of participants were white, which may limit generalisability of results to more diverse populations. In addition, several patient-centered visual function outcomes were reported in a few studies. Pegcetacoplan demonstrated a beneficial effect in slowing the progression of GA but did not show a statistically significant improvement in monocular reading speed or functional reading independence at 24 months versus sham in the OAKS and DERBY trials. Other clinically important outcomes such as contrast sensitivity, reading performance, and vision-related quality of life were infrequently reported, limiting the ability to assess the broader functional benefits of treatment. Finally, formal assessment of publication bias using funnel plots or Egger's regression test was not performed due to the limited number of studies available for quantitative synthesis, in accordance with methodological recommendations. Thus, publication bias cannot be completely excluded.

CONCLUSION(S)

The results of the present study indicate that pegcetacoplan may slow progression of GA in patients with dry AMD as compared to sham, particularly in the first 24 months of treatment. Pegcetacoplan inhibits complement C3 and targets an important pathogenic mechanism driving GA progression and represents a meaningful therapeutic advance for a disease with historically limited treatment options. No significant differences in GA area reduction were observed between PM and PEOM regimens. If efficacy is comparable, then PEOM might be a more practical, less expensive approach than PM. Pegcetacoplan, however, did not significantly improve measures of visual function, including BCVA, monocular reading speed and functional reading independence. Treatment was associated with a significantly increased risk of TEAEs and MNV, while SAEs were more frequent but not significantly different from sham. Clarification of long-term efficacy, functional benefits and safety needs further large-scale studies with longer follow-up.

Authors' contribution: PAA: Conceptualisation, methodology, supervision, resolution of disagreements during study selection and data extraction, statistical analysis, meta-analysis, interpretation of data, manuscript review, and critical revision; DC: Literature search, study selection, data extraction, data curation, statistical analysis, meta-analysis, visualisation, interpretation of data, manuscript drafting, and revision; SSP: Independent study selection, data extraction, validation of extracted data, and manuscript review; RS: Literature search, Independent study selection, data extraction, validation of extracted data, and manuscript review; ND: Methodology, interpretation of findings, manuscript review, and critical editing; BKB: Supervision, interpretation of findings, critical review of the manuscript, and final approval.

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