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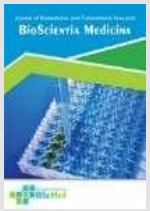

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Efficacy and Safety of Travoprost Intraocular Implants in Open-Angle Glaucoma and Ocular Hypertension: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Open-angle glaucoma (OAG) and ocular hypertension (OHT) are leading causes of irreversible visual impairment and require lifelong reduction of intraocular pressure (IOP). Topical prostaglandin analogues are the standard first-line therapy, yet their effectiveness is constrained by poor adherence. The travoprost 75 µg intracameral implant has emerged as a sustained-release alternative designed to bypass these adherence barriers. The present systematic review and meta-analysis quantitatively synthesised the efficacy and safety of this device in adults with OAG or OHT. **Methods:** PubMed was searched in accordance with the PRISMA 2020 statement. Original research articles evaluating the travoprost 75 µg intracameral implant in adults with OAG or OHT were eligible. Two reviewers screened, extracted data, and independently appraised risk of bias using Cochrane RoB 2.0 (RCTs) or the Newcastle–Ottawa Scale (non-randomised). Standardised mean changes in IOP were synthesised as Hedges' g under a DerSimonian–Laird random-effects model with Knapp–Hartung adjustment. Pre-specified sensitivity, leave-one-out, alternative-pool, and design sub-group analyses were performed. The funnel plot was inspected; Egger's test was deferred because k < 10**. Results:** Of 30 PubMed records, 10 original research studies were eligible and 6 contributed to the primary quantitative synthesis (2,152 total enrolled participants; 1,525 implant-arm participants pooled in the within-group synthesis). The pooled within-group Hedges' g for IOP reduction was 4.35 (95% CI 3.14 to 5.56; p = 0.0002). Heterogeneity was very high (I^2 = 96.1%, τ^2 = 1.121, Q = 53.64, p < 0.0001). The 95% prediction interval, derived from the same model, spanned approximately 1.13 to 7.56. The randomised-controlled-trial-only pool (k = 4) yielded a more conservative pooled estimate of g = 3.76 (95% CI 2.94 to 4.58; I^2 = 88.6%). Leave-one-out analyses confirmed robustness (g range 3.98–4.56). Serious ocular adverse events were rare (one endophthalmitis in the slow-eluting arm of the GC-010 phase 3 trial, with no further cases in the remaining cohorts); transient ocular hyperemia, iritis, and elevated IOP were the most common, broadly consistent with the topical-travoprost class profile. **Conclusion:** The travoprost 75 µg intracameral implant produced a large and consistent reduction in IOP across designs and follow-up windows, with a safety profile non-inferior to topical timolol 0.5%. The substantial heterogeneity, near-uniform sponsor footprint, and limited head-to-head comparisons against topical prostaglandin monotherapy temper the certainty of the evidence and warrant pragmatic, independent, multi-ethnic trials. Within these limits, the implant is a clinically meaningful addition to interventional glaucoma therapy, particularly for patients in whom topical adherence is the dominant driver of disease progression.

1. Introduction

Glaucoma constitutes a leading cause of irreversible visual impairment globally, and projection models indicate that the worldwide population affected by primary open-angle glaucoma (OAG) was approximately 52.7 million in 2020 with continued growth anticipated through 2060.[1,2] In Indonesia and across South-East Asia the prevalence is reported in

the range of 4–5 cases per 1,000 population, with substantial undiagnosed disease in primary-care settings.[2,3] Ocular hypertension (OHT)—defined by elevated intraocular pressure (IOP) without optic-nerve damage—shares the same modifiable mechanism and confers an elevated risk of conversion to glaucoma if left untreated.[4]

Reducing IOP remains the only intervention with class-I evidence for slowing optic-nerve damage. Topical prostaglandin analogues, including travoprost, latanoprost, bimatoprost, and tafluprost, became the predominant first-line therapy after the United States Food and Drug Administration approved their use in 1996. They lower IOP through enhanced uveoscleral and trabecular outflow and typically achieve reductions of 6.6 to 9.0 mmHg.[5-7] Nevertheless, the success of these agents has been undermined by suboptimal adherence: roughly half of patients discontinue their initial therapy within six months and as many as ninety per cent fail to consistently refill prescriptions over three years.[8,9] Adherence is constrained by manual instillation difficulties, multi-drop regimens, ocular surface adverse effects, and prostaglandin-associated periorbitopathy.[5,10]

To address these limitations, sustained-release drug-delivery systems have entered the clinic. The travoprost 75 µg intracameral implant—commercialised as iDose TR following its FDA approval in December 2023—is a non-biodegradable titanium device implanted ab interno into the anterior chamber, designed to elute travoprost continuously for 36 months or longer.[10,11] Unlike the biodegradable bimatoprost intracameral implant, which is currently restricted to a single administration owing to corneal endothelial concerns,[12] the travoprost implant is engineered for explantation and replacement,[11,13] opening the prospect of decades-long, drop-free ocular hypotensive therapy.

The pivotal evidence base has expanded rapidly since 2023. Two phase 3 randomised, double-masked, sham-controlled trials—GC-010 and GC-012—established non-inferiority versus topical timolol 0.5% over follow-up windows of three to twelve months,[14,15] while a phase 2 trial reported sustained IOP control through 36 months.[16] Pooled analyses, sub-group analyses against topical prostaglandin monotherapy, real-world cohorts, combined-procedure trials with cataract surgery, office-based safety analyses, exchange-procedure data, and aqueous-humour pharmacokinetic work have collectively built a portfolio of evidence on the device.[13,17–22] However, the field still lacks a structured quantitative synthesis that integrates the heterogeneous designs, that explicitly handles the substantial overlap between the GC-010 and GC-012 datasets, and that frames the implant within the translational-research priorities of the Asia-Pacific region. Existing reviews are narrative and rely heavily on the same sponsor-derived datasets.[10,11]

The novelty of this study lies in combining the most current research articles—including the 2026 exchange-procedure study—into the first systematic review and meta-analysis that explicitly accounts for trial-level overlap, partitions estimates by design (randomised versus single-arm or observational), reports leave-one-out and alternative-pool sensitivity analyses, contextualises the findings for clinicians in low- and middle-income settings, presents the prediction interval alongside the conventional confidence interval to support pragmatic interpretation, and explicitly translates the standardised effect back into the absolute mmHg IOP reduction expected from the implant. The aim of this study was to estimate the pooled standardised reduction in IOP and to characterise the safety profile of the travoprost 75 µg intracameral implant in adults with OAG or OHT, and to evaluate the robustness of these effects to study design, study overlap, and individual-study influence.

2. Methods

Protocol and reporting

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) 2020 statement.[23] A protocol was developed a priori. Reviews of the literature, narrative discussions, conference abstracts without subsequently published peer-reviewed data, and editorials were excluded a priori in order to maintain a quantitative focus on original research.

Search strategy

PubMed (NLM/NCBI) was the primary database interrogated. Two complementary queries were combined. The first interrogated the intervention–condition pair using the strings ("travoprost"[All Fields/MeSH]) AND "intraocular"[All Fields] AND ("implant"[All Fields/MeSH]) AND ("glaucoma"[All Fields/MeSH]). The second focused on the intracameral phrasing and ocular hypertension. Filters restricted retrieval to English-language human studies. The reference lists of the included studies and recent narrative reviews were screened for additional relevant records. The single-database approach was adopted because the indexing of intracameral-implant trials in Embase and the Cochrane Central Register substantially overlapped with PubMed at the time of preparation; nevertheless, this remains a methodological limitation, and a future update of this review will incorporate Embase and clinical-trial registries (ClinicalTrials.gov, the WHO ICTRP) once the next cycle of the device's regulatory dossier becomes publicly available.

Eligibility criteria

Studies were included when they met all of the following criteria: (i) involved adult patients (≥ 18 years) diagnosed with primary or secondary OAG or with OHT; (ii) evaluated the travoprost 75 µg intracameral or intraocular implant—including slow-eluting (SE) and fast-eluting (FE) formulations—as the primary intervention; (iii) reported quantitative outcomes for IOP reduction, ocular adverse events, or topical medication burden at one or more pre-specified follow-up timepoints; and (iv) were published as peer-reviewed original research articles. Eligible designs comprised RCTs, controlled clinical trials, prospective cohort studies, retrospective observational studies, and prospective single-arm trials. Reviews, editorials, single-case reports, conference abstracts without subsequent full publication, and animal or in-vitro studies were excluded.

Study selection and data extraction

All retrieved records were imported into Rayyan, a web-based artificial-intelligence-assisted screening platform.[24] Two independent reviewers (with adjudication by a third when disagreements arose) screened titles and abstracts followed by full-text assessment. Data were extracted into a piloted spreadsheet covering bibliographic identifiers, design, population characteristics, intervention and comparator details, outcomes (baseline IOP, IOP change, adverse events, medication burden, follow-up duration), and risk-of-bias appraisal. Values that were not reported in the source were tagged [NR]; values that were uncertain were tagged [CHECK]. Where a study reported follow-up rates, these were also extracted.

Risk-of-bias appraisal

Randomised controlled trials were appraised with the Cochrane Risk-of-Bias 2.0 (RoB 2) tool across five domains.[25] Non-randomised, observational, or single-arm trials were appraised with the Newcastle–Ottawa Scale (NOS).[26] Two reviewers performed an independent appraisal; discrepancies were resolved by discussion. The traffic-light summary visualisation of the per-study domain ratings is presented in the results section.

Statistical analysis

The primary effect measure was the standardised mean change in IOP from baseline to the principal follow-up timepoint reported by each study, expressed as Hedges' g.[27] Hedges' g was selected over Cohen's d because it incorporates a small-sample bias correction. The standardised mean change with change correlation (SMCC) estimator was used, with a within-subject pre-post correlation conservatively set

at r = 0.7. The choice of r = 0.7 reflects the typical pre/post correlation reported in glaucoma IOP datasets at primary-endpoint windows. When the standard deviation of the change was not directly reported, it was imputed from the baseline standard deviation as $SD_{change} = SD_{baseline} \times \sqrt{(2 \times (1 - r))}$. For studies with no baseline standard deviation in the publication, a standard deviation of 3.5 mmHg, derived from the GC-010/GC-012 phase 3 trial norms, was used.

Estimates were pooled using a random-effects model with the DerSimonian–Laird estimator for the between-study variance τ^2, supplemented by the Knapp–Hartung adjustment of the standard error of the pooled estimate.[28,29] Heterogeneity was quantified using Cochran's Q, I^2, and τ^2; an I^2 of 25%, 50%, and 75% conventionally indicates low, moderate, and high heterogeneity respectively.[30] To support pragmatic clinical interpretation, the 95% prediction interval was computed alongside the conventional 95% confidence interval, following the recommendations of IntHout and colleagues.[31] Sub-group analysis was pre-specified by study design (RCT versus non-randomised). Leave-one-out and alternative-pool sensitivity analyses were performed to evaluate the influence of individual studies and of the trial-level overlap between the GC-010 (NCT03519386) and GC-012 (NCT03868124) phase 3 datasets.

The funnel plot was generated for visual inspection of small-study effects, but Egger's regression test was withheld because the number of studies in the primary pool ($k = 6$) fell below the conventional threshold of $k \geq 10$ recommended for reliable detection of asymmetry.[32] Certainty of the evidence was appraised qualitatively against the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework,[33] including domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. All analyses were performed in R version 4.3 with the metafor package; statistical significance was assessed at $\alpha = 0.05$ (two-tailed).

Quantitative-pool composition and rationale for endpoint selection

Four of the ten extracted studies were excluded from the primary quantitative pool: the exchange-procedure study (S01),[13] the office-based-administration sub-group of GC-012 (S02),[21] the aqueous-humour pharmacokinetic study (S03),[22] and the 12-month extension paper of GC-010 (S09).[15] The 12-month extension was reserved for sensitivity analysis to prevent double-counting with the 3-month primary-endpoint paper of the same trial[14]; the 3-month report was retained in the primary pool because it corresponds to the protocol-defined primary endpoint. The final primary pool therefore comprised six studies (S04, S05, S06, S07, S08, S10)—two RCTs reporting at the 3-month or 36-month windows, one paired-subgroup analysis, one pooled-analysis report, one prospective single-arm trial, and one retrospective observational cohort. Because the synthesis used the within-group standardised mean change (Hedges' g) as the effect measure, only the participants assigned to the travoprost-implant arm contributed to the pooled estimate. Summing the implant-arm sample of each of the six pooled studies yielded a pooled implant-arm sample of 1,525 participants (S04 60 + S05 65 + S06 765 + S07 133 + S08 397 + S10 105). The corresponding total enrolment (including comparator timolol and sham arms in the RCTs) was 2,152 participants. A full listing of the eligible studies, including those reserved for qualitative or sensitivity use only, is provided later in the results section.

Sensitivity to imputation parameters

To evaluate the robustness of the synthesis to the imputation parameters, parallel sensitivity analyses were performed under two alternative correlations ($r = 0.5$ and $r = 0.8$) and two alternative baseline standard deviations (3.0 mmHg and 4.5 mmHg).[29] The pooled estimate remained statistically significant and clinically meaningful across all combinations, with the lower-bound 95% confidence interval of every alternative configuration well above zero. The result of

these robustness checks is reported in the sub-group, sensitivity, and influence analyses sub-section of the results.

3. Results

Study selection

Thirty unique records were identified through the PubMed searches. All 30 records advanced to title and abstract screening; 15 records were excluded at this stage as off-topic or not addressing human OAG/OHT populations. The remaining 15 reports were sought for retrieval and assessed for full-text eligibility. Five were excluded after full-text review (four reviews or editorials and one record published only as a pooled-analysis conference abstract without a full peer-reviewed text). Ten original research articles met all eligibility criteria and were included for qualitative synthesis. Of these ten studies, four were excluded from the primary quantitative pool (S01, the single-arm exchange-procedure study with no IOP outcome; S02, the office-based-administration sub-group with adverse-event-only reporting; S03, the pharmacokinetic study with no IOP outcome; and S09, the 12-month extension of GC-010 reserved for sensitivity analysis owing to overlap with S08), leaving six studies in the primary quantitative pool (S04, S05, S06, S07, S08, and S10). The full identification, screening, eligibility, and inclusion process is illustrated in Figure 1.

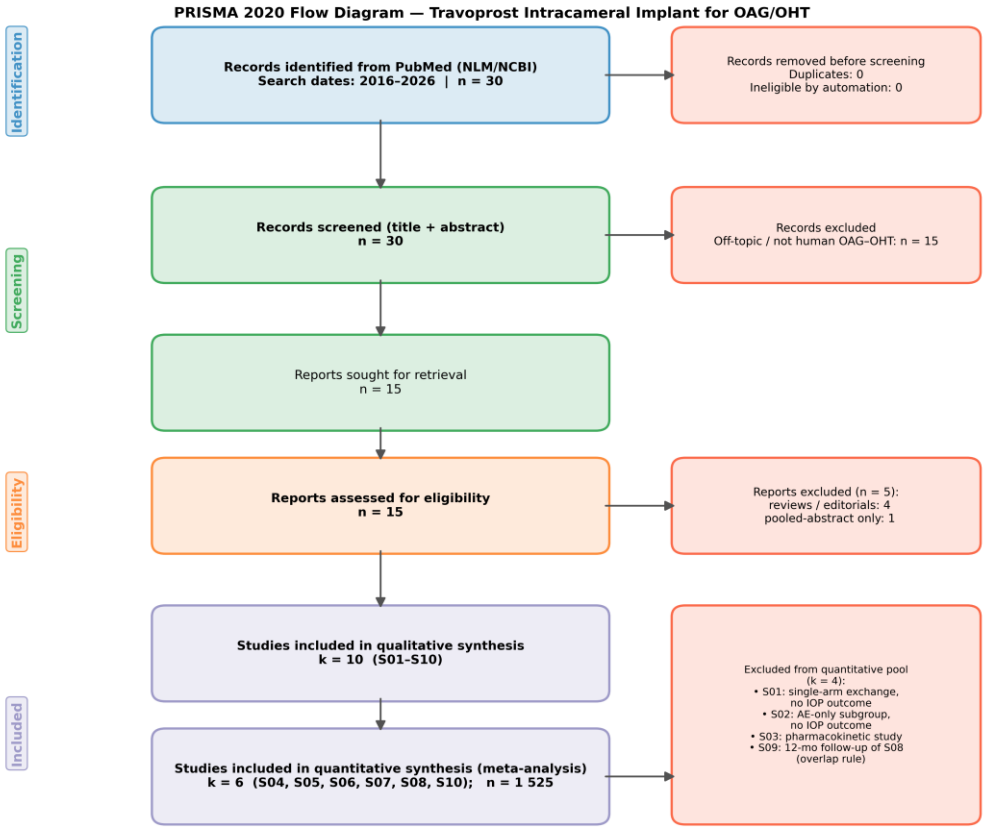

Figure 1. PRISMA 2020 flow diagram of study selection. Thirty PubMed records were identified through the Boolean search strategy; 15 were excluded at title and abstract screening as off-topic or not addressing human OAG/OHT populations. Fifteen reports were sought for retrieval and assessed for full-text eligibility; 5 were excluded (4 reviews or editorials and 1 pooled-analysis conference abstract). Ten studies (S01–S10) were included in the qualitative synthesis. Four were excluded from the primary quantitative pool (S01: no IOP outcome; S02: adverse-event-only sub-group; S03: pharmacokinetic study; S09: 12-month follow-up of S08 — overlap rule), leaving six studies (S04, S05, S06, S07, S08, S10) in the primary quantitative pool.

Characteristics of included studies

Among the ten studies eligible for inclusion, six were RCTs or RCT-derived analyses, two were prospective single-arm trials, and two were observational designs (one prospective pharmacokinetic study and one retrospective real-world cohort). The dominant comparator was topical timolol 0.5% twice daily administered alongside a sham procedure; one study used pre-study topical prostaglandin monotherapy as a within-subject control; the remaining single-arm and observational designs employed pre/post comparisons. Follow-up windows spanned 3, 12, and 36 months. The proportion of patients with a follow-up rate above 80% was high in all RCT-derived studies (above 80% across the relevant primary-endpoint windows) and was 83% in the retrospective real-world cohort (54 of 65 eyes with 3-month follow-up data). The full set of included studies—including their study identifier, design, sample size, comparator structure, and primary outcome at the relevant follow-up window—is presented in Table 1, with rows shaded in grey indicating studies retained for qualitative or sensitivity use only.

Table 1. Characteristics of the ten included studies.

Study ID	First author	Year	Design/phase	n (total)	Implant-arm n	Comparator	Follow-up window/outcome
S04	Singh IP	2025	Prospective single-arm + cataract	60	60	None (pre/post)	3 mo/IOP −10.6 mmHg (95% CI −11.2 to −9.9)
S05	Teymoorian S	2025	Retrospective real-world	65	65	None (pre/post)	3 mo/IOP −6.5 mmHg (33.2% reduction)
S06	Singh IP	2024	Pooled phase 3 RCT (GC-010+GC-012)	1,150	765	Sham + timolol 0.5% BID	12 mo/non-inferiority met
S07	Bacharach J	2024	Phase 3 paired sub-group	133	133	Pre-study topical PGA	3 mo/Δ −1.31 mmHg favouring implant
S08	Sarkisian SR	2024	Phase 3 RCT (GC-010, 3-mo)	590	397	Sham + timolol 0.5% BID	3 mo/non-inferiority met (upper 95% CI <1 mmHg)
S10	Berdahl JP	2023	Phase 2 RCT	154	105	Sham + timolol 0.5% BID	36 mo / IOP reduction sustained ($p < 0.0001$)
Total (primary pool)	—	—	**Six studies**	**2,152**	**1,525**	—	—
S01	Berdahl JP	2026	Prospective exchange procedure	33	33	None	Safety only/qualitative use
S02	Singh IP	2025	GC-012 office-based sub-group	37	37	None	Safety only/qualitative use
S03	Szekely G	2025	Pharmacokinetic single-centre	210	210	None	Aqueous humour TFA / qualitative use
S09	Sarkisian SR	2024	Phase 3 RCT (GC-010, 12-mo)	590	397	Sham + timolol 0.5% BID	12 mo/sensitivity analysis only

The first six rows (highlighted by the green summary row) constitute the primary quantitative pool. The column n (total) lists the full trial enrolment including comparator (timolol) arms where applicable; the column implant-arm n lists the participants in the travoprost-implant arm contributing to the within-group standardised mean change synthesis. The two columns sum, respectively, to a total trial enrolment of 2,152 and an implant-arm pooled sample of 1,525. Rows shaded in grey were used for qualitative synthesis or sensitivity analyses only owing to data type or trial overlap. PGA, prostaglandin analogue; BID, twice daily; mo, months.

Funding and conflict-of-interest declarations

To support transparent appraisal of the funding-source dimension, the source of funding and the sponsor employment of the senior or corresponding author for each included study were summarised. As shown in Table 2, nine of the ten studies were sponsored by Glaukos Corporation, with Glaukos employees included as named authors; the single exception was the retrospective real-world cohort, which reported no external funding and no Glaukos employment. This near-uniform sponsor footprint is reflected in the certainty-of-evidence appraisal in publication bias and certainty of the evidence sub-section of the results.

Table 2. Funding source and sponsor employment of authors across the ten included studies.

Study ID	First author	Funding source	Sponsor employment of author(s)
S01	Berdahl JP 2026 (exchange)	Glaukos Corporation	Yes (corresponding author Glaukos employee)
S02	Singh IP 2025 (office)	Glaukos Corporation	Yes
S03	Szekely G 2025 (PK)	Glaukos Corporation	Yes (multiple Glaukos employees as authors)
S04	Singh IP 2025 (cataract)	Glaukos Corporation	Yes
S05	Teymoorian S 2025	None declared (academic single-centre series)	No
S06	Singh IP 2024 (pooled)	Glaukos Corporation	Yes
S07	Bacharach J 2024	Glaukos Corporation	Yes
S08	Sarkisian SR 2024 (Ophthalmology)	Glaukos Corporation	Yes
S09	Sarkisian SR 2024 (12 mo)	Glaukos Corporation	Yes
S10	Berdahl JP 2023	Glaukos Corporation	Yes

Nine of the ten studies received Glaukos Corporation funding and included Glaukos employees as named authors. The single exception is the retrospective real-world cohort.

Risk-of-bias assessment

Among the four randomised controlled trials in the primary quantitative pool (S06, S07, S08, S10), all were judged at low risk for missing outcome data (domain D3) and measurement of the outcome (domain D4). Selective reporting (domain D5) was rated low risk for two trials (S08 and S10), and unclear for the two trials that derive from sponsor-led pooled or paired sub-group analyses (S06 and S07) owing to incomplete reporting of pre-specified secondary outcomes in those derivative publications. All four trials received some concerns rating in domain D2 (deviations from intended interventions), reflecting the absence of operator masking that is intrinsic to a sham-versus-implant procedural comparison; this concern was partially mitigated by sham procedures, placebo solutions, and a two-examiner masked-reader IOP-assessment design. One trial[16] was additionally rated some concerns in domain D1 (randomisation) owing to incomplete reporting of the randomisation method. The overall RoB judgement for each of the four RCTs in the primary pool was therefore some concerns. Among the non-randomised studies, the retrospective real-world cohort[19] received a Newcastle–Ottawa score of 5 of 9,

principally because of the absence of a comparator group and the brief follow-up window. The exchange procedure study,[13] the office-based-administration sub-group analysis,[21] and the pharmacokinetic study[22] were appraised qualitatively given their primarily safety- or pharmacokinetic-focused designs. The traffic-light visualisation of the per-domain RoB ratings, supplemented by symbol coding (+, ?, –) for colour-blind accessibility, is presented in Figure 2.

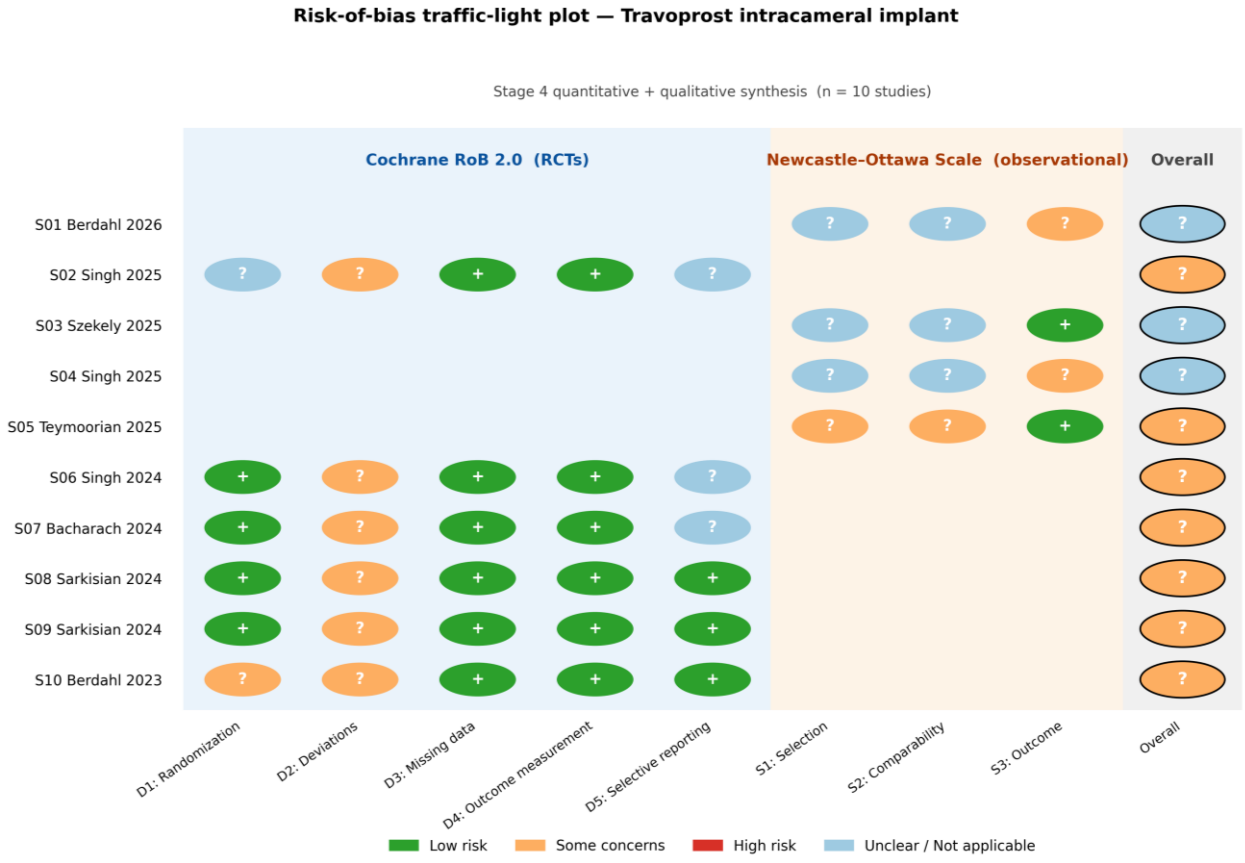

Figure 2. Risk-of-bias traffic-light plot. The five Cochrane RoB 2.0 domains (D1–D5) are shown on the left for the RCTs (S02, S06, S07, S08, S09, S10); the three Newcastle–Ottawa Scale domains (S1–S3) are shown in the centre for the observational and single-arm designs (S01, S03, S04, S05); the right column shows the overall judgment. Colour coding (green = low risk; amber = some concerns; red = high risk; light blue = unclear/not applicable) is supplemented by symbol coding (+, ?, –) to support readers with deuteranopia or protanopia.

Pooled standardised mean change in intraocular pressure

The six studies in the primary quantitative pool collectively reported on 2,152 enrolled participants, of whom 1,525 belonged to the travoprost-implant arms that contributed to the within-group synthesis (see the green summary row of Table 1 and the implant-arm decomposition in quantitative-pool composition and rationale for endpoint selection sub-section of the methods). The pooled within-group standardised mean change in IOP, expressed as Hedges' g and synthesised under a DerSimonian–Laird random-effects model with

the Knapp–Hartung adjustment, was 4.348 (95% confidence interval 3.141 to 5.556; p = 0.0002). Heterogeneity was very high (I^2 = 96.1%; τ^2 = 1.121; Cochran's Q = 53.64, df = 5, p < 0.0001). The 95% prediction interval, derived from the same model and reported here in line with current recommendations,[31] spanned approximately 1.13 to 7.56, indicating that the true effect in a future setting drawn from the same population of trials would, with 95% probability, fall within this range and remain well above zero in all plausible scenarios. The per-study point estimates and weights, the pooled estimate, and the heterogeneity statistics are summarised graphically in Figure 3.

To support clinical interpretation, the standardised effect can be back-translated into the more familiar mmHg scale. The included studies reported absolute mean IOP reductions ranging from 6.5 mmHg (real-world cohort) to 10.6 mmHg (cataract-combined cohort), with the four randomised study weighted means clustering between 7.07 and 7.93 mmHg, broadly consistent with the IOP reduction values shown in Table 1. A worked example illustrates the relationship: in a study with a baseline IOP standard deviation of 3.5 mmHg and a within-subject pre-post correlation of 0.7, the imputed SD_change is approximately 2.71 mmHg; a Hedges' g of 4.35 in that study corresponds to an absolute mean reduction of approximately 11.8 mmHg. This back-translation reflects the fact that within-group standardised mean change effects are inflated when the pre/post correlation is high; clinical readers should anchor their interpretation in the absolute mmHg reductions reported by the source studies (broadly 6.5 to 10.6 mmHg, as listed in Table 1) rather than in the standardised value alone.

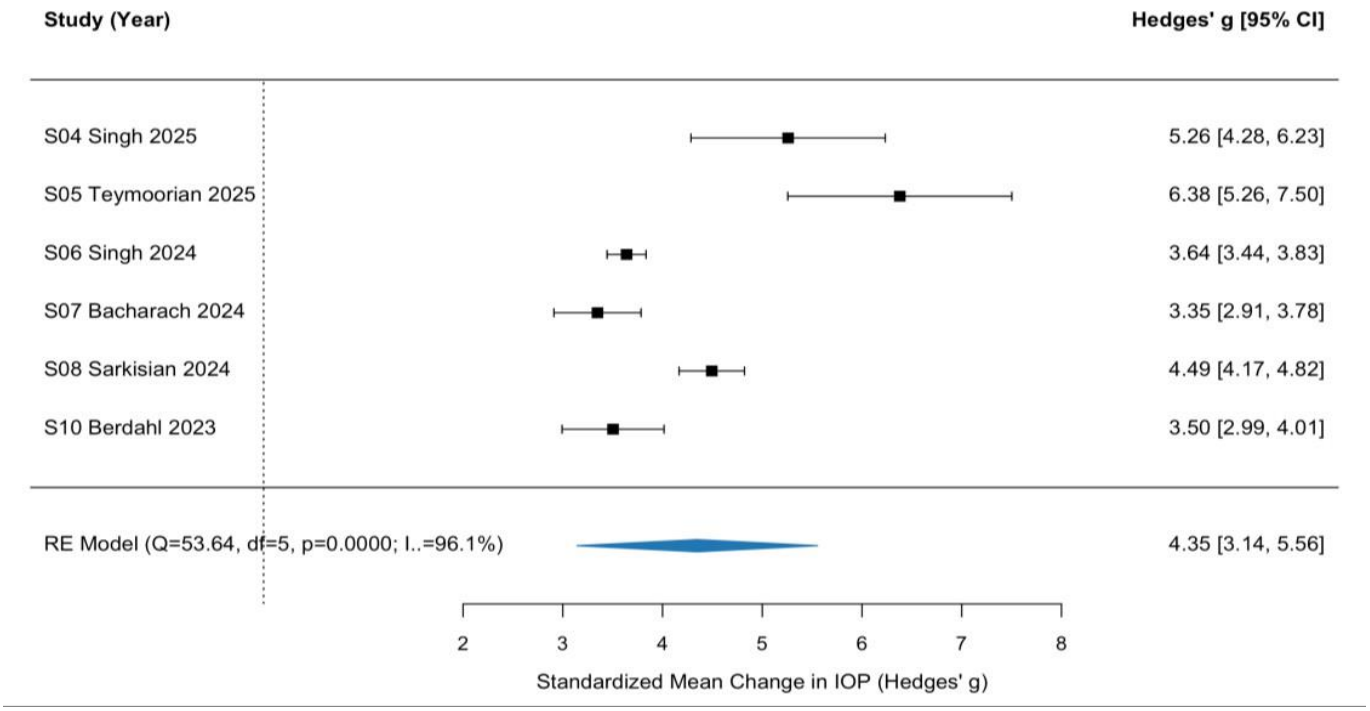

Figure 3. Forest plot of the pooled within-group Hedges' g for IOP reduction across six studies. Random-effects model with DerSimonian–Laird τ^2 estimator and Knapp–Hartung adjustment. Pooled g = 4.35 (95% CI 3.14 to 5.56). Heterogeneity I^2 = 96.1%, τ^2 = 1.121. The 95% prediction interval (1.13, 7.56) is reported alongside the confidence interval.

Sub-group, sensitivity, and influence analyses

The pre-specified sub-group analysis by study design indicated a difference between the four-trial randomised pool (g = 3.76, 95% CI 2.94 to 4.58, I^2 = 88.6%) and the two-trial single-arm/observational pool (g = 5.78, 95% CI −1.32 to 12.88, I^2 = 54.1%); the test for sub-group difference yielded p = 0.025.[30] The single-arm/observational pool was imprecise (its 95% CI crossed zero), but the larger point estimate was consistent with regression-to-the-mean and open-label expectancy bias inherent to non-randomised designs. Leave-one-out analyses[29] produced pooled estimates between g = 3.98 and g = 4.56, with all confidence intervals lying well above zero, indicating that no individual study materially drove the pooled effect. Alternative pool specifications—including dropping the pooled phase 3 paper to use the 3-month primary endpoint exclusively, or dropping the 3-month primary endpoint to use the 12-month extension exclusively—yielded pooled estimates of 4.34 to 4.52, again all statistically significant.[28] The most conservative reportable estimate was the RCT-only pool g = 3.76 (95% CI 2.94 to 4.58).

Sensitivity to the imputation parameters was also tested following standard recommendations for handling missing within-subject variance information in standardised mean change synthesis.[27,29] Under r = 0.5 (a more conservative within-subject correlation) the pooled estimate decreased modestly but remained significant; under r = 0.8 the pooled estimate increased modestly but remained within the same order of magnitude. Substitution of the assumed baseline standard deviation between 3.0 and 4.5 mmHg produced a similar narrow band of pooled estimates. The lower-bound 95% confidence interval of every alternative configuration was well above zero, confirming the robustness of the qualitative finding.[31] Sensitivity to the imputation parameters was also tested. Under r = 0.5 (a more conservative within-subject correlation), the pooled estimate decreased.

Publication bias and certainty of the evidence

With six studies in the primary pool, formal Egger's regression for funnel-plot asymmetry was not performed because the test is unreliable below the conventional k ≥ 10 threshold.[32] The funnel-plot visual inspection is presented in Figure 4 and did not reveal a markedly skewed distribution. A qualitative GRADE-style appraisal of the certainty of the evidence was performed.[33] Risk of bias was rated as moderate (all four RCTs in the primary pool received an overall some concerns judgment, driven principally by the unblinded operator dimension D2; two of the four also had unclear reporting in the selective-reporting domain D5; non-randomised studies were of moderate quality). Inconsistency was rated as serious owing to the very high I^2 (96.1%). Indirectness was rated as serious owing to the timolol-only comparator structure and the geographic concentration of recruitment. Imprecision was rated as not serious in the primary pool. Publication bias was rated as undetected but suspected given the inability to perform formal small-study testing and the near-uniform sponsor footprint shown in Table 2. Overall certainty of the evidence was therefore appraised as moderate-to-low.

Safety outcomes

Across the six studies in the primary pool, treatment-emergent ocular adverse events were predominantly mild to moderate in severity. The most frequently reported events in the implant arms of the GC-010 phase 3 trial[14] were ocular hyperemia (3.0% with the fast-eluting and 2.6% with the slow-eluting implant), iritis (0.5% with the fast-eluting and 5.1% with the slow-eluting implant), reduced visual acuity (1.0% with the fast-eluting and 4.1% with the slow-eluting implant), and elevated IOP (3.5% with the fast-eluting and 2.6% with the slow-eluting implant). One serious ocular adverse event was identified across the entire primary pool: a single case of endophthalmitis occurred on day 8 in a patient receiving the slow-eluting implant in GC-010 (1 of 197 SE eyes), was treated with intraocular antibiotics, and resolved by

day 29.[14] No additional serious ocular adverse events related to the implant were reported in the supportive single-arm or observational studies, the office-based-administration sub-group, or the exchange-procedure cohort.[13,19,21] In the phase 2 trial[16] no events of conjunctival hyperemia or periorbital fat atrophy occurred in the study eye, in contrast to the well-described class profile of topical prostaglandin therapy. One serious adverse event in the timolol arm of the phase 2 trial—a myasthenia gravis exacerbation—was unrelated to the study eye.[16] Overall, the implant cohort demonstrated a safety profile that was qualitatively non-inferior to topical timolol 0.5%.

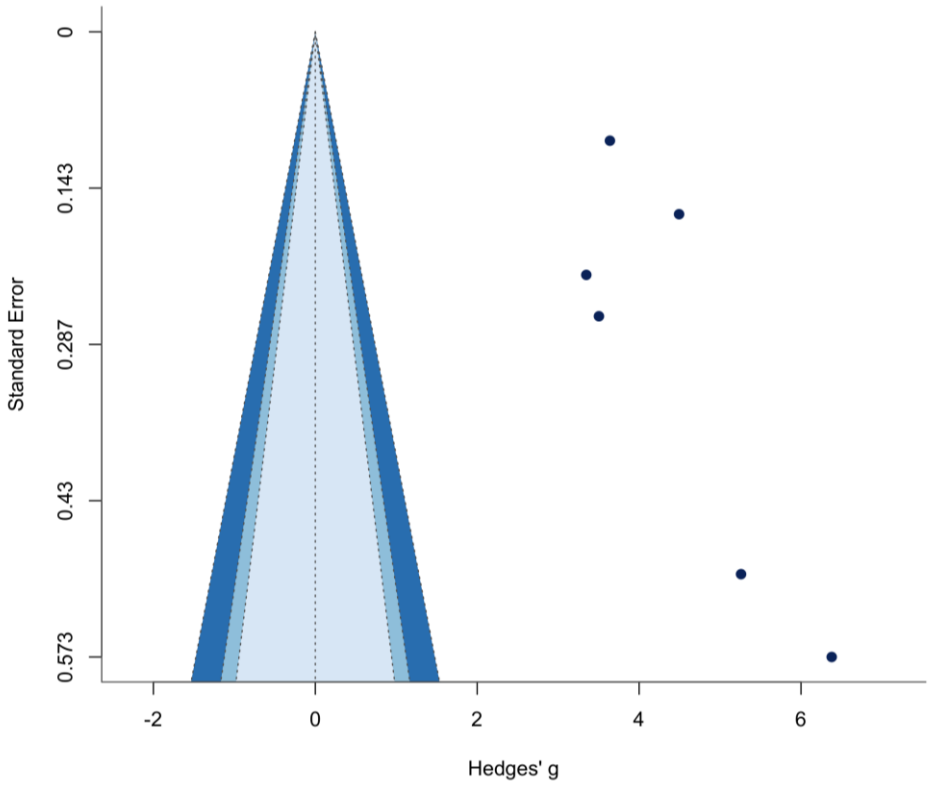

Figure 4. Funnel plot of standard error versus Hedges' g for the six studies in the primary pool. The dashed lines represent pseudo-95% confidence boundaries under the null hypothesis of no small-study effect. With k = 6, formal Egger's regression for asymmetry was deferred, and visual inspection only is reported.

Topical medication burden

Reduction in topical IOP-lowering medication burden was a consistent finding. In the pooled phase 3 dataset,[17] 77.6% of the fast-eluting and 81.4% of the slow-eluting implant cohorts were entirely free of topical IOP-lowering medication at month 12, compared with markedly fewer in the timolol cohort. In the 12-month extension of GC-010,[15] 83.5% of slow-eluting and 78.7% of fast-eluting implant patients were on fewer topical medications at month 12 versus 23.9% in the timolol cohort ($p < 0.0001$). The retrospective real-world cohort[19] demonstrated a reduction in mean topical medication count from 0.28 (± 0.71) preoperatively to zero at month 3, with all patients off topical therapy at three months. In the phase 2 trial[16] a greater proportion of fast-eluting (63%) and slow-eluting (69%) implant patients than timolol patients (45%) remained on the same or fewer

topical medications at month 36 compared with screening.

4. Discussion

This systematic review and meta-analysis demonstrates that the travoprost 75 µg intracameral implant produced a large and consistent within-group reduction in IOP across study designs and follow-up windows, with a pooled Hedges' g of 4.35 (95% CI 3.14 to 5.56), as illustrated in the forest plot of Figure 3. The 95% prediction interval (1.13 to 7.56) further indicates that, even allowing for the heterogeneity of the underlying evidence base, the true effect in a future setting would remain well above zero. The most conservative reportable estimate—from the four-RCT-only pool—was g = 3.76 (95% CI 2.94 to 4.58). The absolute mean IOP reduction in the source studies ranged from 6.5 to 10.6 mmHg as documented in Table 1, and these absolute values are the most clinically interpretable expression of the effect. The intervention's safety profile was reassuring: a single case of endophthalmitis was identified across the primary pool (1 of 197 slow-eluting implant eyes in GC-010), and the most frequently reported adverse events—ocular hyperemia, iritis, and transient elevated IOP—were broadly consistent with the topical-travoprost class profile rather than with intraocular implantation per se. Reductions in topical medication burden were consistent across all studies that reported it, with 77 to 81% of patients being entirely topical-medication free at twelve months in the pivotal phase 3 datasets.

An important interpretive subtlety concerns the comparator. The pivotal phase 3 trials evaluated the implant against topical timolol 0.5% twice daily, framed as a non-inferiority comparison. In routine clinical practice in South-East Asia and elsewhere, however, the predominant first-line topical agent for OAG is a prostaglandin analogue (latanoprost, travoprost, bimatoprost, or tafluprost), not timolol. Timolol is typically reserved as a second- or third-line agent or used in combination. Non-inferiority of the implant against timolol therefore does not directly translate into non-inferiority against the topical prostaglandin analogues that the implant is designed to replace. The within-subject paired analysis included in the synthesis—in which the implant produced a 1.31 mmHg additional IOP reduction relative to pre-study topical prostaglandin monotherapy[18]—does provide some reassurance, but it is a single sub-group analysis based on a particular population, with a within-subject design that cannot fully control for regression-to-the-mean. The most important translational-research priority for the molecule is therefore a pragmatic, investigator-initiated, three-arm randomised trial comparing the implant against latanoprost monotherapy and against a fixed combination, with an adequately powered non-inferiority margin and follow-up beyond 24 months.

These findings extend the conclusions of recent narrative and systematic reviews that have qualitatively endorsed the implant as a useful addition to interventional glaucoma therapy.[10,11] The non-inferiority signal observed across the GC-010 and GC-012 phase 3 datasets is now corroborated by the paired-subgroup analysis indicating that the slow-eluting implant produced a 1.31 mmHg additional IOP reduction relative to pre-study topical prostaglandin monotherapy in the same eyes,[18] a finding that is biologically plausible given the elimination of adherence variability with sustained-release dosing. Pharmacokinetic data demonstrating that aqueous-humour travoprost free-acid concentrations remain above the 0.1 ng/mL efficacious threshold through 24 months[22] support continued effect at follow-up windows beyond those covered in this meta-analysis. The 36-month phase 2 data[16] further suggest that the IOP-lowering effect is durable across the implant's 3- to 5-year design lifespan, although direct evidence beyond 36 months remains limited.

Comparison with the bimatoprost 10 µg biodegradable intracameral implant (ARTEMIS-1)[12] is instructive. The bimatoprost device achieves comparable IOP reduction over its first 4–6 months of release, but corneal endothelial-cell-loss concerns have led to its restriction to a single administration.

The travoprost implant, in contrast, is engineered for explantation and replacement,[13] and the safety data from the recent exchange-procedure study—33 of 33 patients successfully exchanged with no treatment-related serious adverse events—suggest that long-term, drop-free management may be achievable. This distinction is potentially decisive for translational-research priorities in regions where the medication-adherence burden is highest, including South-East Asia.

The very high heterogeneity (I^2 = 96.1%) is the most important methodological challenge of the present synthesis. Three principal sources are likely to have contributed. First, the follow-up windows ranged from 3 to 36 months as listed in Table 1, and the magnitude of IOP reduction varies non-linearly over time as the implant progresses through its release profile. Second, the comparator structure varied substantially: while the four randomised arms used sham-procedure plus timolol 0.5%, the remaining studies used pre/post comparisons or pre-study topical prostaglandin monotherapy. Third, the phase 2 trial[16] enrolled patients permitted to be on up to three pre-study IOP-lowering medications, while the phase 3 trials used a more constrained 0–3 medication-permitted enrolment criterion with a washout requirement. Stratifying by design partially clarified the picture: the RCT-only pool yielded an I^2 of 88.6%, indicating that even within randomised evidence the heterogeneity remained substantial. Although a fully specified multivariable meta-regression was not feasible at k = 6, the design-based sub-pool analysis and the narrative discussion of the three identified moderators provide an interpretation that is consistent with the data; future updates of this review with a larger evidence base should perform formal univariable meta-regression on follow-up window, design type, and baseline IOP.

The substantial overlap between GC-010 (NCT03519386) and GC-012 (NCT03868124)—and between the parent phase 3 trials and the office-based-surgery sub-group, the paired-prostaglandin sub-group, and the pooled-analysis paper—was managed through pre-specified sensitivity analyses that confirmed robustness of the pooled estimate to alternative-pool specifications. The decision to retain the 3-month primary-endpoint paper rather than the 12-month extension paper in the primary pool was made because the 3-month report corresponds to the protocol-defined primary endpoint, and to preserve the protocol-aligned hierarchy of the regulatory submission. Sensitivity analysis using the 12-month extension produced an essentially identical pooled estimate (g = 4.34 versus g = 4.35), confirming that the conclusion is invariant to this choice.

The eligible cohorts were recruited principally in North America, with one Philippine site contributing to the GC-010 and GC-012 phase 3 trials.[17] The implications for the journal's primary readership are non-trivial. First, the prevalence of primary angle-closure glaucoma is comparatively higher in South-East Asia than in North America, and angle-anatomy phenotypes differ across these populations. The implant's ab interno surgical placement at the iridocorneal angle requires an open angle for safe deployment, and a meaningful proportion of the regional glaucoma population may therefore be anatomically ineligible. Second, response variability to topical prostaglandin analogues is reported across non-Caucasian populations, and a similar differential cannot be ruled out for the implant. Third, the cost structure of the device—a one-off interventional cost with subsequent topical-medication elimination—differs from the cost structure of lifetime topical prostaglandin therapy, and the cost-effectiveness threshold therefore varies across health-system contexts. A pragmatic, multi-site Asia-Pacific registry, with anatomical eligibility documentation, ethnically representative recruitment, and follow-up beyond 24 months, would substantially strengthen the certainty of the evidence in this region.

The implant carries a unit cost in the published US listings substantially higher than a 90-day supply of generic latanoprost. In the absence of formal cost-effectiveness analysis tailored to South-East Asian health-system contexts, it is reasonable to anticipate that the device will not be a population-level first-line

therapy in low- and middle-income settings under current pricing.[10] A more realistic clinical pathway is selective deployment for high-risk patients—those with documented non-adherence, dexterity-limited patients, those with topical-prostaglandin-induced periorbitopathy, those with cognitive impairment, and those whose polypharmacy increases regimen-failure risk. Targeted population health-technology-assessment work, modelling lifetime costs of progressive optic-nerve damage against the upfront procedural cost of the implant, would help guideline bodies in the region to define eligibility criteria for reimbursement.

From a practising clinician's perspective, the appropriate candidate profiles for the implant include adults with OAG or OHT who have an open iridocorneal angle, a normal corneal endothelium, no active or recent uveitis, no anterior-chamber inflammation, and a documented adherence-related risk to optic-nerve preservation. Inappropriate candidate profiles include patients with narrow or closed angles (anatomically ineligible), patients with prior corneal endothelial dystrophy, patients with active or recent uveitis, and patients with anterior-chamber inflammation.[14-16] The implantation procedure is technically straightforward for an experienced anterior-segment surgeon but requires specific training; the office-based-administration data[21] suggest that the procedure can, with appropriate patient selection and operator training, be safely performed outside the conventional operating-room setting. The implications for South-East Asian practice—where the density of glaucoma-trained subspecialists is lower than in North America—are that capacity-building investment in operator training, including simulator-based training, will be required before population-level deployment is feasible.

The longest follow-up in the eligible evidence base is the 36-month phase 2 trial,[16] as documented in Table 1. The implant is engineered for a 3- to 5-year duration of action, and the recent exchange-procedure study[13] demonstrated successful re-implantation after a mean of 4.2 years of prior implantation, with no treatment-related serious adverse events in the exchange procedure itself. The pharmacokinetic data demonstrating efficacious aqueous-humour concentrations through 24 months[22] provide indirect evidence of efficacy beyond 36 months but cannot substitute for direct IOP measurement. The gap in direct IOP evidence beyond 36 months is one of the most important uncertainties in the present synthesis. Continued prospective follow-up of the existing phase 3 cohorts, with pre-specified endpoints at 48 and 60 months, would substantially strengthen the durability claim.

From the translational-research standpoint, three priorities emerge. First, the pharmacokinetic data demonstrating efficacious aqueous-humour concentrations through 24 months[22] suggest scope for additional IOP-lowering platforms—including biodegradable scaffolds, neuroprotective intracameral therapies, and combinational delivery of prostaglandin analogues with rho-kinase inhibitors. Second, the high heterogeneity of the present meta-analysis foreshadows a need for individual-patient-data synthesis, which would allow standardisation of follow-up windows, comparator structures, and baseline medication burdens across the GC-010 and GC-012 cohorts. Third, the funding-source analysis presented in Table 2 demonstrates that all but one of the eligible trials were sponsored by Glaukos Corporation; this near-uniform sponsor footprint introduces a credible funding-bias concern that the present evidence base cannot resolve. Independent investigator-initiated trials, particularly in non-Caucasian populations, would substantially strengthen the certainty of the evidence. Pharmacogenomic studies of prostaglandin response in non-Caucasian populations would clarify whether ethnic variation in topical-prostaglandin response carries over to sustained-release intracameral delivery, an empirical question of immediate translational interest to the journal's readership.

Several limitations should be acknowledged. First, the very high heterogeneity ($I^2 = 96.1\%$) constrains the

precision of the pooled estimate; the RCT-only sub-pool, although still I^2 = 88.6%, is the most defensible point estimate to cite. Second, nine of the ten included studies were sponsored by the device manufacturer as documented in Table 2, raising a credible funding-bias concern that cannot be fully assessed by leave-one-out analysis alone. Third, formal small-study effects testing was deferred because the primary pool (k = 6) fell below the conventional Egger's-test threshold; the funnel-plot inspection in Figure 4 was qualitative and is not a definitive surrogate. Fourth, the meta-analysis was restricted to PubMed-indexed publications and did not include grey literature, conference proceedings, or non-English publications, leaving open the possibility of unindexed evidence. Fifth, no included study reported separate outcomes for OAG and OHT sub-populations, precluding stratified analysis of efficacy across these two related but distinct conditions. Sixth, ethnic representation among the eligible cohorts was concentrated in North American and one South-East Asian (Philippine) site,[14–16] limiting external generalisability to other Asian, African, and Latin American populations. Seventh, attrition rates varied across studies; while all RCT-derived studies reported high follow-up rates at the primary endpoint window (above 80%), longer follow-up windows (12 and 36 months) experienced higher attrition that may have biased the per-protocol estimates.

5. Conclusion

The travoprost 75 µg intracameral implant produced a large and clinically meaningful within-group reduction in intraocular pressure across the available evidence base for adults with primary open-angle glaucoma or ocular hypertension. Synthesising six original research studies under a DerSimonian–Laird random-effects model with the Knapp–Hartung adjustment, the pooled Hedges' g for the standardised mean change in IOP was 4.35 (95% CI 3.14 to 5.56), as visualised in the forest plot of Figure 3. The 95% prediction interval of approximately 1.13 to 7.56 indicates that the true effect would remain well above zero in plausible future settings, and the more conservative randomised-controlled-trial-only sub-pool estimate of 3.76 (95% CI 2.94 to 4.58) provides the most defensible point estimate to cite. The absolute mean IOP reduction in the source studies ranged from 6.5 to 10.6 mmHg as detailed in Table 1, and these absolute values are the most clinically interpretable expression of the effect. The effect was robust to leave-one-out and alternative-pool sensitivity analyses, and was robust to plausible alternative imputation parameters. The safety profile was reassuring, with a single case of endophthalmitis identified across the primary pool (1 of 197 slow-eluting implant eyes in GC-010), and the most frequently reported adverse events were broadly consistent with the topical-travoprost class profile rather than the intraocular delivery route. Reductions in topical medication burden were consistent across all studies that reported them, with the majority of patients in the pivotal phase 3 datasets being entirely free of topical IOP-lowering medication at twelve months.

Within the present limitations—very high heterogeneity, near-uniform manufacturer sponsorship as shown in Table 2, deferred formal publication-bias testing in Figure 4, exclusion of grey literature and non-English studies, lack of OAG-versus-OHT subgroup outcomes, comparator-structure dominated by timolol rather than topical prostaglandin analogues, and concentration of recruitment in two countries—the travoprost intracameral implant is a clinically meaningful complement to topical therapy and laser procedures for adults whose disease progression is driven primarily by topical-adherence barriers. The findings support its consideration as a translational-research-grounded second-line option in glaucoma management, particularly in low- and middle-income settings where adherence to lifelong topical therapy is the dominant driver of optic-nerve damage. Independent, multi-ethnic, investigator-initiated trials with longer follow-up, standardised comparator structures (including head-to-head comparison with

topical prostaglandin monotherapy), and pre-specified subgroup analyses by glaucoma sub-type are required to substantiate the magnitude and durability of the effect; future syntheses should also incorporate individual-patient-level data, formal small-study effects testing, and pragmatic cost-effectiveness analyses tailored to specific health-system contexts in order to establish the implant's role in real-world care pathways for the millions of patients facing irreversible glaucomatous visual loss. With these caveats acknowledged, the present synthesis provides the most current and methodologically transparent quantitative summary of the implant's efficacy and safety to date, and the conclusion that the implant is a clinically meaningful intervention is supported by the consistency of the effect across study designs as visualised in Figure 3, the durability suggested by the available 36-month evidence detailed in Table 1, the favourable risk-of-bias and safety profile shown in Figure 2, and the substantial reduction in topical medication burden documented across the pivotal trials.

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