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Efficacy and Safety of Perfluorohexyloctane Eye Drops for Dry Eye Disease: A Systematic Review and Meta-Analysis

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Efficacy and Safety of Perfluorohexyloctane Eye Drops for Dry Eye Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Dry eye disease (DED) is one of the most common ocular surface disorders worldwide, yet current treatments remain limited in their ability to simultaneously improve both signs and symptoms. Perfluorohexyloctane is a novel, preservative-free, water-free semifluorinated alkane eye drop that stabilizes the tear film lipid layer. We conducted this systematic review and meta-analysis to evaluate the efficacy and safety of perfluorohexyloctane eye drops for the treatment of DED.

Methods: We searched PubMed, EMbase, Cochrane Library, Web of Science, CNKI, and Wanfang databases from inception to May 2026 for randomized controlled trials evaluating perfluorohexyloctane for DED. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane RoB 2.0 tool. Meta-analyses were performed using RevMan 5.4. Evidence quality was graded using the GRADE system.

Results: Five studies comprising 1,913 patients were included. Perfluorohexyloctane significantly improved total corneal fluorescein staining at Week 8 (MD = -1.11, 95% CI: -1.36 to -0.86, $P < 0.00001$, $I^2 = 0\%$), eye dryness visual analog scale score (MD = -10.28, 95% CI: -12.59 to -7.96, $P < 0.00001$, $I^2 = 0\%$), and OSDI score (MD = -5.49, 95% CI: -7.70 to -3.28, $P < 0.0001$, $I^2 = 0\%$). Efficacy began at Week 2 (MD = -0.59) and increased through Week 8 (MD = -1.11). Total adverse events did not differ from control (RR = 1.05, 95% CI: 0.81 to 1.35, P = 0.91). Blurred vision was more frequent in the perfluorohexyloctane group (RR = 4.32, 95% CI: 1.65 to 11.36, P = 0.003) but all events were mild and transient. GRADE ratings were high for the primary outcomes.

Conclusions: Perfluorohexyloctane eye drops effectively reduce corneal epithelial damage and dry eye symptoms, with effects from Week 2 through Week 8, and have a favorable safety profile. These findings support perfluorohexyloctane as an effective treatment option for DED.

Keywords: perfluorohexyloctane; dry eye disease; systematic review; meta-analysis; randomized controlled trial.

1 Introduction

Dry eye disease (DED) ranks among the most prevalent ocular surface disorders worldwide, affecting 21%–30% of the Chinese population and 5%–50% of individuals globally [1,2]. The condition arises from disrupted tear film homeostasis and presents with persistent ocular discomfort and visual symptoms that substantially compromise daily functioning and work efficiency [3].The prevalence continues to rise due to population aging, prolonged screen time, and environmental factors. DED has become a major public health concern worldwide [4,5].

DED pathophysiology is driven by interrelated factors including tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory dysfunction [6]. Available treatments—artificial tears, anti-inflammatory drugs, and physical modalities—offer incomplete relief. While artificial tears are the most commonly used option, they provide only transient symptomatic improvement without correcting the root causes. Lipid-containing artificial tears can cause transient blurred vision and reduce patient adherence [7]. Anti-inflammatory agents such as cyclosporine and lifitegrast can reduce ocular surface inflammation. However, they have a slow onset of action (weeks to months). Some patients discontinue treatment due to instillation site reactions [8,9]. Physical therapies such as warm compresses, meibomian gland massage, and intense pulsed light are effective but require specialized equipment and are inconvenient for patients [10,11]. Therefore, a novel therapy with rapid onset, dual efficacy on signs and symptoms, and good tolerability is urgently needed.

Perfluorohexyloctane (NOV03 in the US, SHR8058 in China) is a water-free, preservative-free semifluorinated alkane [12]. Its action is twofold. The compound spreads rapidly across the cornea owing to its low surface tension and assembles into a protective supramolecular film at the tear‑air interface, minimizing evaporative water loss [13]. In parallel, it enters the meibomian glands and may facilitate recovery of their lipid-secreting capacity [14]. Several phase 2 and phase 3 clinical trials have demonstrated the efficacy and safety of perfluorohexyloctane for DED [15–19].

Although individual clinical trials have reported positive results, these studies differ in patient populations, comparator choices, and effect sizes. A comprehensive systematic review and meta-analysis based on all available RCT evidence is lacking. This study aimed to systematically evaluate the efficacy and safety of perfluorohexyloctane for DED and to provide high-level evidence for clinical decision-making.

2 Methods

2.1 Registration and Reporting

This study protocol was registered on PROSPERO (CRD42025631761). The report follows the PRISMA 2020 statement [20] and the Cochrane Handbook for Systematic Reviews of Interventions [21].

2.2 Inclusion and Exclusion Criteria

2.2.1 Study Type

Randomized controlled trials (RCTs), regardless of blinding.

2.2.2 Participants

Eligible participants were adults (≥18 years) who met the diagnostic criteria for DED (summarized in Table 1).

2.2.3 Interventions

Experimental group: perfluorohexyloctane eye drops (NOV03/SHR8058), twice or four times daily. Control group: saline solution (0.6% or 0.9% NaCl).

2.2.4 Outcomes

Primary outcomes: (1) Change from baseline in tCFS score; (2) Change from baseline in eye dryness VAS score (0–100).

Secondary outcomes: (1) Change from baseline in OSDI score; (2) tCFS responder rate (≥3-point improvement from baseline); (3) Eye dryness VAS responder rate (≥30% reduction from baseline); (4) Adverse event rate.

2.2.5 Exclusion Criteria

Non-RCT studies; duplicate publications; studies with non-extractable data; animal or

basic research studies.

2.3 Search Strategy

Literature searches were executed in PubMed, EMbase, Cochrane Library, Web of Science, CNKI, and Wanfang from database inception through May 2026. The search strategy combined MeSH terms and keywords related to perfluorohexyloctane and dry eye disease.("perfluorohexyloctane," "NOV03," "SHR8058," "dry eye," "dry eye disease," "keratoconjunctivitis sicca," "meibomian gland dysfunction," and "randomized controlled trial.")

2.4 Study Selection and Data Extraction

Two reviewers independently screened studies and extracted data. Disagreements were resolved through discussion or consultation with a third reviewer. Extracted data included: study characteristics (first author, publication year, country, design), participant characteristics (sample size, age, sex, baseline disease severity), intervention details (drug name, dosage, frequency, duration), comparator details, outcome data (change values, standard deviations, between-group differences with 95% CIs), safety data, and subgroup data. For studies reporting only LSMean differences and 95% CIs without group means and SDs, we directly extracted the LSMean differences and standard errors (SEs). For studies reporting group means and SDs, we preferentially extracted between-group MDs and 95% CIs. For studies reporting only P values without 95% CIs, we performed descriptive analysis only without quantitative synthesis. SEs were calculated as: SE = (CI upper bound − CI lower bound) / (2 × 1.96).

2.5 Risk of Bias Assessment

Risk of bias was appraised using Cochrane's RoB 2.0 instrument [21], which evaluates five domains—randomization, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Each domain was rated as low risk, some concerns, or high risk, with the overall rating derived from domain-level judgments.

2.6 Statistical Analysis

All meta-analyses were performed using RevMan 5.4. Continuous outcomes were pooled using mean differences (MDs) with 95% confidence intervals (CIs), while binary outcomes were summarized as risk ratios (RRs) with 95% CIs. Between-study

heterogeneity was quantified using the I^2 statistic and the Chi^2 test. A fixed-effect model was applied when heterogeneity was low ($I^2 \leq 50\%$ and $P \geq 0.10$); otherwise, a random-effects model was used. Sources of heterogeneity were explored when indicated. Statistical significance was set at $P < 0.05$.

2.7 Sensitivity Analysis

The influence of each study on the pooled estimate was evaluated via leave-one-out sensitivity analysis, conducted using the metaninf routine in Stata 18.0 [22]. For the primary outcomes (tCFS, eye dryness VAS), we also pooled results using both fixed-effect and random-effects models to assess the impact of model choice.

We performed cumulative meta-analysis by adding studies chronologically by publication year. This allowed us to observe how the pooled effect estimate evolved as evidence accumulated. Cumulative analyses were implemented in Stata 18.0 using the metacum command [23,24].

We performed meta-regression to explore potential sources of heterogeneity. Publication year was used as the covariate to assess its effect on the pooled effect size. Meta-regression was implemented in Stata 18.0 using the metareg command [25]. A P-value < 0.05 was considered statistically significant.

2.8 Publication Bias Assessment

We used funnel plots (generated by RevMan 5.4) and Galbraith radial plots (generated by Stata 18.0 using the galbraith command) to assess publication bias and small-study effects [26,27]. Funnel plots were inspected visually for symmetry. Galbraith plots were used to identify potential outlier studies by comparing each study's point with the $z = \pm 2$ regression lines. Because fewer than 10 studies were included, we did not perform Egger's regression test.

2.9 Quality of Evidence

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to rate the quality of evidence for the primary outcomes [28,29]. Evidence was classified as high, moderate, low, or very low.

3 Results

3.1 Study Selection

The initial search yielded 367 records (PubMed: 60, Web of Science: 133, EMBASE: 144, Cochrane Library: 30, CNKI and Wanfang: 0). After deduplication, 86 records remained. We excluded 66 records after screening titles and abstracts (post-hoc analyses: 6, reviews: 4, duplicates: 7, animal studies: 2, cell studies: 4, irrelevant studies: 38, case reports: 1, conference abstracts: 3, and other reasons: 1). Twenty records proceeded to full-text review. After full-text review, we excluded 15 records (single-arm studies: 9, conference abstracts: 4, not the study drug: 1, and non-placebo control: 1). Five studies were finally included for qualitative and quantitative synthesis [13,15–18]. The screening process is shown in Figure 1.

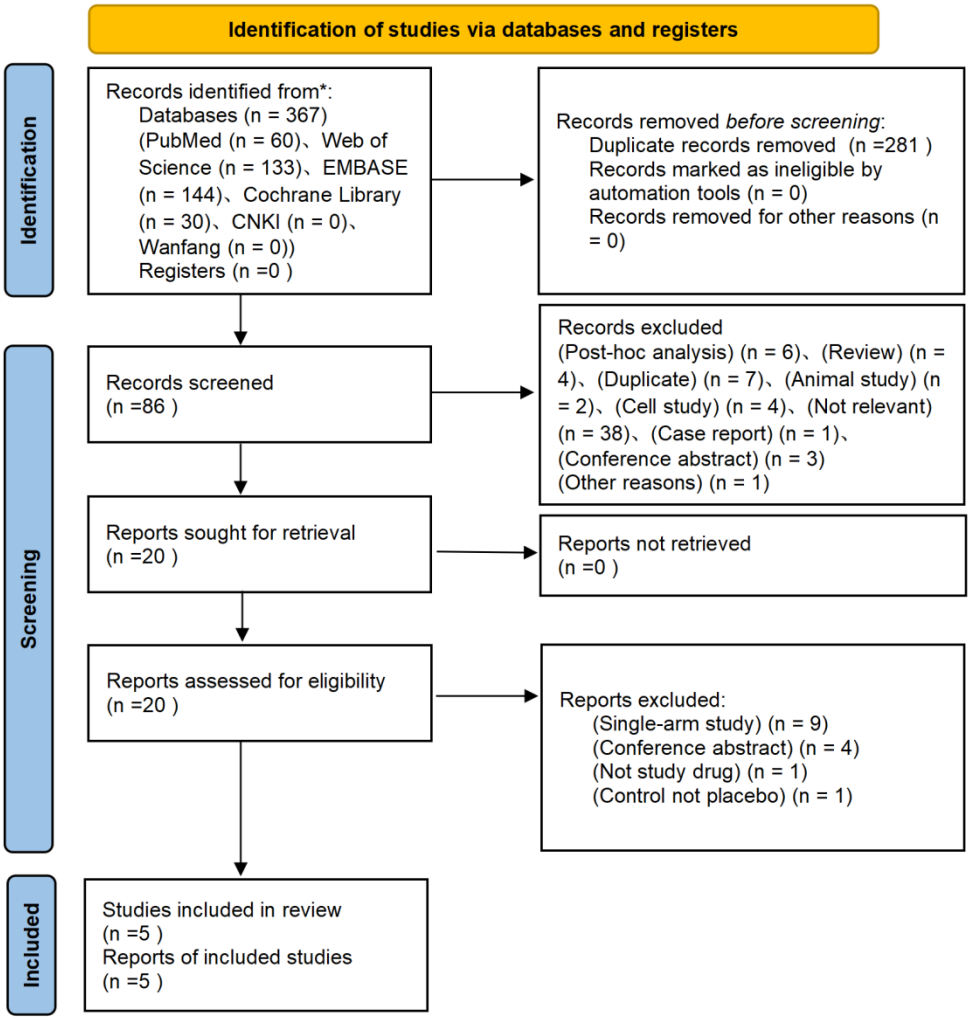


Figure 1. PRISMA 2020 flow diagram of study selection process.

3.2 Characteristics of Included Studies

The five included studies comprised 1,913 patients (1,019 in the perfluorohexyloctane group and 894 in the control group). The characteristics of each study are shown in

169 Table 1.

Table 1. Characteristics of included studies

Study ID	Study design	Registration (NCT)	Follow-up (weeks)	Country	N randomized (I/C)	Diagnostic criteria	Intervention	Comparator	Outcomes assessed
Tian 2023[15]	Phase 3, RCT, DB, MC	NCT05515471	8	China	156 / 156	OSDI≥25; TFBUT≤ 5s; Schirmer≥5mm; tCFS 4-11; MGD≥3	SHR8058 (Perfluorohexyl octane) QID	0.6% NaCl	①②③④ ⑤⑥⑦
Tauber 2023[16]	Phase 3, RCT, DB, MC	NCT04139798	8	USA	303 / 294	OSDI≥25; TFBUT≤ 5s; Schirmer≥5mm; tCFS 4-11; MGD≥3	NOV03 (Perfluorohexyl octane) QID	0.6% NaCl (with BAK)	①②⑦
Sheppard 2023[17]	Phase 3, RCT, DB, MC	NCT04567329	8	USA	311 / 309	OSDI≥25; TFBUT≤ 5s; Schirmer≥5mm; tCFS 4-11; MGD≥3	NOV03 (Perfluorohexyl octane) QID	0.6% NaCl (with BAK)	①②③⑦
Tauber 2021[18]	Phase 2, RCT, DB, MC	NCT03333057	8	USA	114(QID)、 111(BID)/111	OSDI≥25; TFBUT≤ 5s; Schirmer≥5mm; tCFS 4-11; MGD≥3	NOV03 QID / NOV03 BID	0.9% NaCl	①②③⑦
Schmidl 2020[13]	Phase 2, RCT, SB, observer-blinded	NCT03048526	4	Austria	24 / 24	TFBUT≤10s; Schirmer 5-15mm; VAS≥20	Perfluorohexyl octane QID	0.9% NaCl (unpreserved)	③④⑦⑧ ⑨

170 Abbreviations: RCT, randomized controlled trial; DB, double-masked; MC, multicenter; SB, single-masked; QID, four times
171 daily; BID, twice daily; OSDI, Ocular Surface Disease Index; TFBUT, tear film breakup time; tCFS, total corneal fluorescein
172 staining; MGD, meibomian gland dysfunction; VAS, visual analog scale; BAK, benzalkonium chloride. ① tCFS change from
173 baseline; ② Eye dryness VAS change from baseline; ③ OSDI change from baseline; ④ TFBUT change from baseline; ⑤
174 MGD score change from baseline; ⑥ Schirmer I test change from baseline; ⑦ Adverse events; ⑧ TFT (tear film thickness);
175 ⑨ LLT (lipid layer thickness).

Baseline characteristics are presented in Table 2. Age, sex, baseline tCFS, eye dryness VAS, OSDI, MGD score, TFBUT, and Schirmer I test results were comparable across groups.

Table 2. Baseline demographic and clinical characteristics of included studies

Study ID	N (I/C)	Age, mean (SD), years	Female, n (%)	Disease duration, mean (SD), months	Baseline tCFS, mean (SD)	Baseline Eye dryness VAS, mean (SD)	Baseline OSDI, mean (SD)	Baseline MGD score, mean (SD)	Baseline TFBUT, mean (SD), s	Baseline Schirmer I, mean (SD), mm
Tian 2023[15]	156 / 156	45.4 (15.2) / 43.7 (15.1)	118 (75.6) / 127 (81.4)	16.0 (12.0-30.0)† / 24.0 (12.0-36.0)†	6.2 (1.9) / 6.3 (1.7)	64.7 (15.1) / 65.6 (16.5)	55.8 (16.6) / 56.2 (16.6)	8.4 (3.7) / 8.4 (3.8)	2.97 (0.90) / 2.88 (0.91)	12.9 (7.0) / 13.2 (7.0)
Tauber 2023[16]	303 / 294	60.3 (20-87)* / 61.6 (19-88)*	219 (72.3) / 214 (72.8)	NR	6.7 (1.8) / 6.7 (1.9)	66.5 (19.1) / 66.8 (18.7)	53.9 (17.6) / 54.4 (17.0)	7.4 (3.1) / 7.7 (3.2)	3.2 (0.8) / 3.3 (0.8)	12.0 (8.3) / 11.7 (7.6)
Sheppard 2023[17]	311 / 309	53.3 (19-85)* / 53.8 (20-88)*	250 (80.4) / 238 (77.0)	NR	7.0 (2.0) / 7.1 (2.1)	64.7 (19.5) / 64.3 (19.8)	55.2 (17.4) / 55.8 (17.2)	7.9 (3.5) / 8.1 (3.5)	3.2 (0.9) / 3.1 (0.9)	12.7 (7.5) / 12.8 (7.9)
Tauber 2021 [18]	114 / 111	53.0 (22-86)* / 53.8 (19-85)*	79 (69.3) / 80 (72.1)	NR	7.0 (2.2) / 6.7 (2.0)	68.6 (21.8) / 66.8 (21.7)	55.3 (17.4) / 54.0 (16.9)	7.6 (3.5) / 8.0 (3.9)	3.0 (0.93) / 3.0 (0.91)	14.6 (8.9) / 14.3 (8.8)
Schmidl 2020[13]	24 / 24	37.5 (12.5)‡	18 (75.0)‡	NR	NR	NR	44 (22) / 40 (14)	NR	3.7 (1.7) / 3.8 (2.1)	10.5 / 9.1

Abbreviations: SD, standard deviation; I, intervention group; C, control group; NR, not reported; QID, four times daily; BID, twice daily; tCFS, total corneal fluorescein staining; VAS, visual analog scale; OSDI, Ocular Surface Disease Index; MGD, meibomian gland dysfunction; TFBUT, tear film breakup time. Data presented as mean (range). † Data presented as median (interquartile range). ‡ Data presented as overall population (mean ± SD). For Tauber 2021, only QID data are presented in the baseline table; BID data are not included in the primary efficacy analysis.

3.3 Risk of Bias Assessment

We assessed the risk of bias for the five studies using the Cochrane RoB 2.0 tool

(Figure 2). Tian 2023, Tauber 2023, Sheppard 2023, and Tauber 2021 were rated as low risk across all five domains. Schmidl 2020 was rated as having "some concerns" overall due to its single-masked design (Domain 2). This did not affect the reliability of the main conclusions, as this study did not contribute to the primary efficacy meta-analyses.

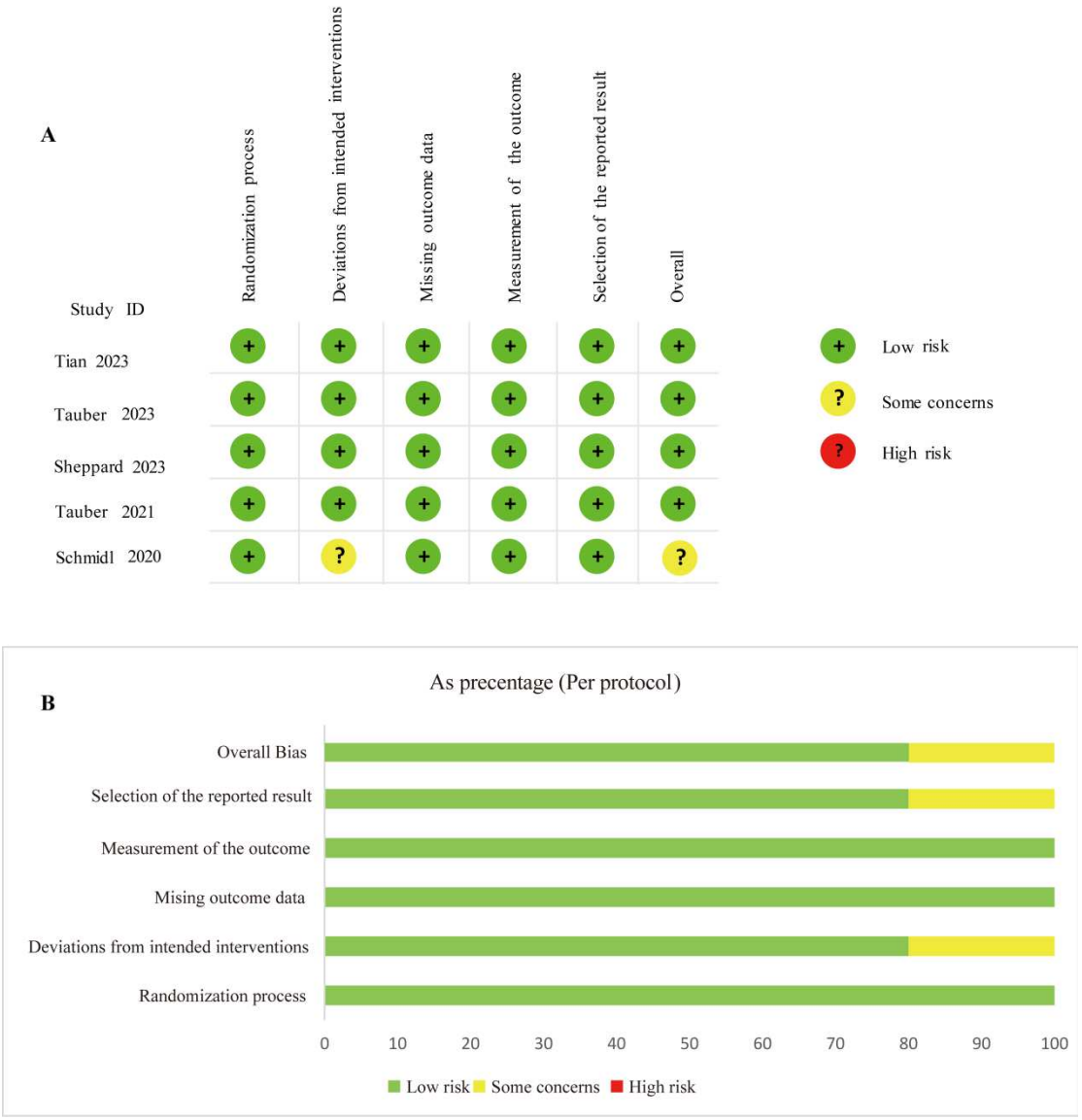


Figure 2. Risk of bias assessment using the Cochrane RoB 2.0 tool. (a) Risk of bias summary for each included study; (b) Risk of bias graph presenting the proportion of studies with low, some concerns, and high risk across each domain.

3.4 Meta-Analysis Results

3.4.1 tCFS Score Change (Primary Outcome)

Four registration trials [15–18] reported changes in tCFS score from baseline to Week

8. A total of 1,754 patients were included. The meta-analysis showed no significant heterogeneity (I^2 = 0%, P = 0.89). We used a fixed-effect model. Perfluorohexyloctane significantly improved tCFS score compared with control (MD = -1.11, 95% CI: -1.36 to -0.86, P < 0.00001) (Figure 3). This effect size exceeded the minimal clinically important difference for tCFS (MCID = 1.0) [30], indicating clinical significance.

Time-point subgroup analysis showed that the treatment effect emerged at Week 2 (MD = -0.59, 95% CI: -0.80 to -0.38, P < 0.00001, I^2 = 0%), continued to improve at Week 4 (MD = -0.91, 95% CI: -1.58 to -0.25, P < 0.00001, I^2 = 63%), and reached its maximum at Week 8 (MD = -1.11, 95% CI: -1.36 to -0.86, P < 0.00001, I^2 = 0%). This pattern shows a clear time–effect relationship. The Week 4 analysis included only two studies. The I^2 estimate was therefore unstable. We used a random-effects model for this subgroup.

Corneal region subgroup analysis showed that perfluorohexyloctane significantly protected both the inferior region (2 studies, MD = -0.29, 95% CI: -0.43 to -0.16, P < 0.0001, I^2 = 0%) and the temporal region (2 studies, MD = -0.28, 95% CI: -0.44 to -0.12, P = 0.0008, I^2 = 0%). Effect sizes were similar across regions, suggesting that the drug acts across the entire ocular surface rather than at specific focal points.

We also explored potential effect modifiers by dosing frequency (QID vs. BID), region (USA vs. China vs. Austria), and trial phase (phase 2 vs. phase 3). However, BID data were only available from Tauber 2021. China data were only available from Tian 2023. Phase 2 data were only available from Tauber 2021. Each of these subgroups contained only one study. Meaningful between-subgroup comparisons could not be performed. Therefore, these stratified analyses are not presented as forest plots. We report them descriptively: the QID effect size (MD = -1.11) was numerically larger than the BID effect size (MD = -0.85). The effect sizes for the USA (3 studies pooled, MD = -1.10) and China (MD = -1.14) were similar. The effect sizes for phase 3 trials (3 studies pooled, MD = -1.09) and the phase 2 trial (MD = -1.18) were directionally consistent. These exploratory findings should be interpreted cautiously due to the limited number of studies in each stratum.

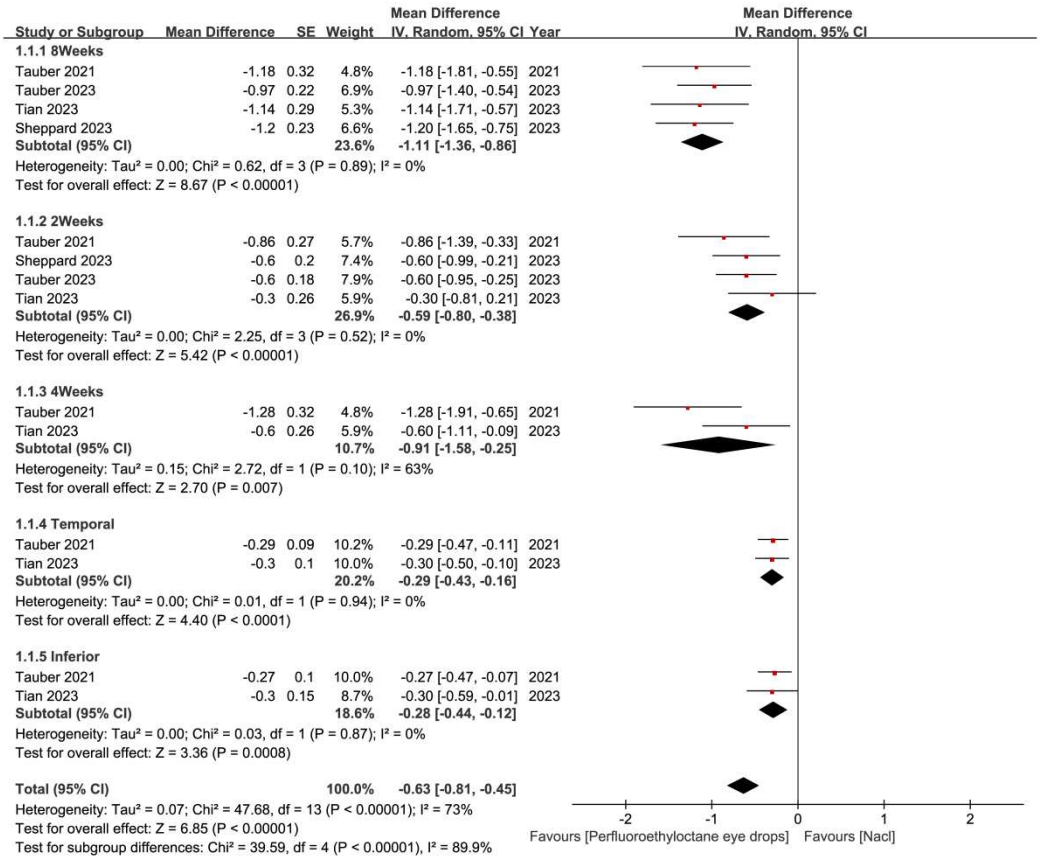


Figure 3. Forest plots of tCFS outcomes. (a) tCFS change from baseline at Week 8 (primary analysis, 4 studies); (b) Subgroup analysis by follow-up time (Week 2, Week 4, and Week 8); (c) Subgroup analysis by corneal region (inferior and temporal). tCFS, total corneal fluorescein staining (NEI scale, 0 – 15); MD, mean difference; CI, confidence interval; IV, inverse variance; QID, four times daily; Random, random-effects model; Fixed, fixed-effect model. The pooled MD for Week 8 was -1.11 (95% CI: -1.36 to -0.86, $P < 0.00001$, $I^2 = 0\%$), exceeding the MCID threshold of 1.0. A random-effects model was applied for the Week 4 subgroup ($I^2 = 63\%$, only 2 studies). Horizontal lines represent 95% CIs; diamonds represent pooled estimates.

3.4.2 Eye Dryness VAS Score Change (Primary Outcome)

Five studies [13,15–18] reported changes in eye dryness VAS score from baseline. The meta-analysis showed no significant heterogeneity ($I^2 = 0\%$, $P = 0.40$). We used a fixed-effect model. Perfluorohexyloctane significantly improved eye dryness VAS score compared with control (MD = -10.28, 95% CI: -12.59 to -7.96, $P < 0.00001$) (Figure 4A).

In a sensitivity analysis, we included the estimated data from Schmidl 2020 (4-week follow-up, MD ≈ -1.0). The pooled effect remained significant (MD = -9.28, 95% CI:

-13.34 to -3.46, P = 0.0009). However, heterogeneity increased substantially (I^2 = 85%). This was attributable to the much smaller effect size in Schmidl 2020 compared with the other four studies. The shorter follow-up (4 weeks vs. 8 weeks) and the estimation method may explain this difference (Figure 4B). Excluding this study restored the heterogeneity to I^2 = 0%, confirming the robustness of the main analysis.

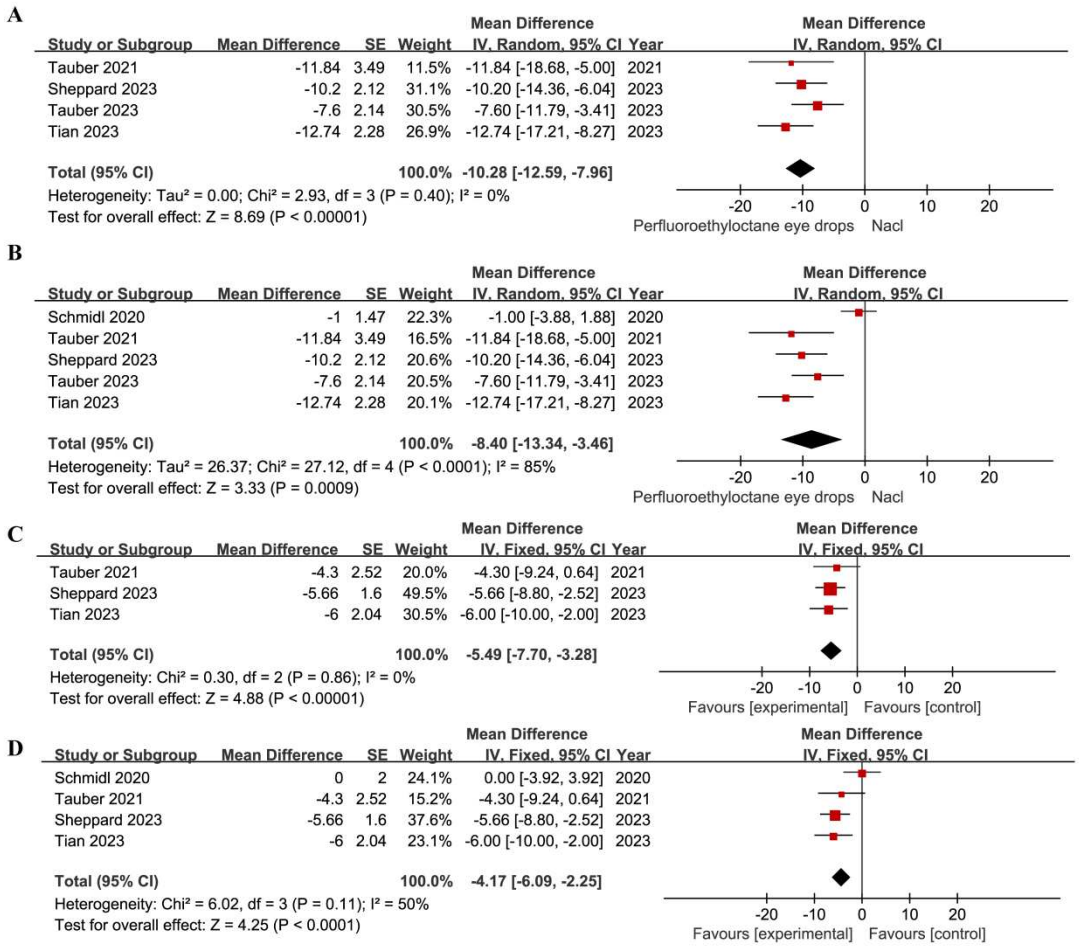


Figure 4. Forest plots of secondary efficacy outcomes. (a) Eye dryness VAS change from baseline at Week 8 (primary analysis, 4 studies); (b) Eye dryness VAS change from baseline (sensitivity analysis including Schmidl 2020); (c) OSDI change from baseline at Week 8 (primary analysis, 3 studies); (d) OSDI change from baseline (sensitivity analysis including Schmidl 2020). VAS, visual analog scale (0 – 100); OSDI, Ocular Surface Disease Index (0 – 100); MD, mean difference; CI, confidence interval; IV, inverse variance; QID, four times daily. The primary VAS analysis (I^2 = 0%) included 4 registration trials; the sensitivity analysis adding Schmidl 2020 increased I^2 to 85%. The primary OSDI analysis (I^2 = 0%) included 3 studies; the sensitivity analysis adding Schmidl 2020 (MD ≈ 0) increased I^2 to 50%.

3.4.3 OSDI Score Change (Secondary Outcome)

Three studies [15,17,18] reported changes in OSDI score from baseline to Week 8. The meta-analysis showed no significant heterogeneity ($I^2 = 0\%$, $P = 0.86$). We used a fixed-effect model. Perfluorohexyloctane significantly improved OSDI score compared with control (MD = -5.49, 95% CI: -7.70 to -3.28, $P < 0.00001$) (Figure 4C).

In a sensitivity analysis including Schmidl 2020 (MD = 0), the pooled effect remained significant (MD = -4.17, 95% CI: -6.09 to -2.25, $P < 0.0001$). Heterogeneity increased slightly ($I^2 = 50\%$), mainly due to the null effect in Schmidl 2020 (Figure 4D). This further supported the robustness of the primary analysis.

3.4.4 Responder Rates

Three studies [15–17] reported tCFS responder rates (≥3-point improvement). Perfluorohexyloctane showed significantly higher responder rates than control (73.1%, 41.2%, 50.0% vs. 55.1%, 27.2%, 30.7%). The pooled RR was 1.49 (95% CI: 1.33 to 1.68, $P < 0.00001$, $I^2 = 21\%$) (Figure 5A).

Three studies [15–17] reported eye dryness VAS responder rates (≥30% reduction). Perfluorohexyloctane also showed significantly higher rates than control (81.4%, 57.4%, 65.6% vs. 66.0%, 46.6%, 45.3%). The pooled RR was 1.31 (95% CI: 1.20 to 1.43, $P < 0.00001$, $I^2 = 40\%$) (Figure 5B).

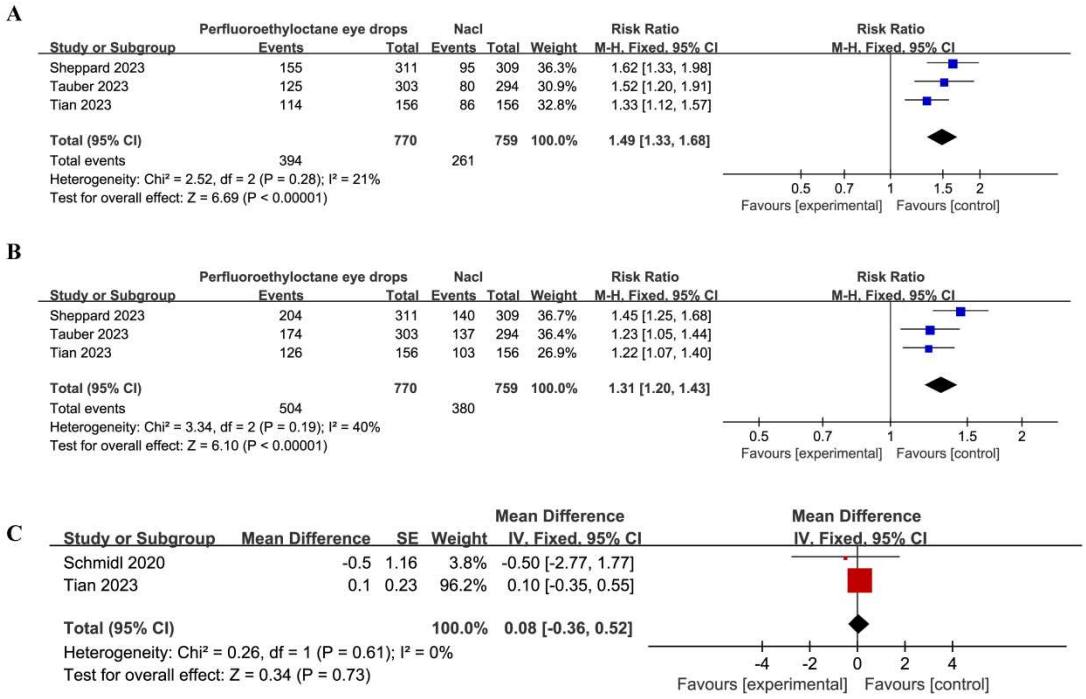


Figure 5. Forest plots of responder rates and exploratory TFBUT analysis. (a) tCFS responder rate

at Week 8 (≥3-step improvement); (b) Eye dryness VAS responder rate at Week 8 (≥30% reduction); (c) TFBUT change from baseline (exploratory analysis). RR, risk ratio; CI, confidence interval; M-H, Mantel-Haenszel; TFBUT, tear film breakup time; MD, mean difference. Responder analyses were based on 3 studies (Tian 2023, Tauber 2023, Sheppard 2023). The pooled RR for tCFS responders was 1.49 (95% CI: 1.33 to 1.68, P < 0.00001, I^2 = 21%). The pooled RR for VAS responders was 1.31 (95% CI: 1.20 to 1.43, P < 0.00001, I^2 = 40%). TFBUT analysis included only 2 studies (Tian 2023 and Schmidl 2020); the pooled MD was 0.08 seconds (95% CI: -0.36 to 0.52, P = 0.73, I^2 = 0%).

3.4.5 Tear Film Breakup Time

Only two studies [13,15] reported TFBUT change data. Schmidl 2020 provided estimated data. The pooled estimate was not statistically significant (MD = 0.08, 95% CI: -0.36 to 0.52, P = 0.73, I^2 = 0%) (Figure 5C). Given the limited number of studies reporting TFBUT and the known high variability and low repeatability of TFBUT measurements, this result should be interpreted cautiously and does not affect the main conclusions.

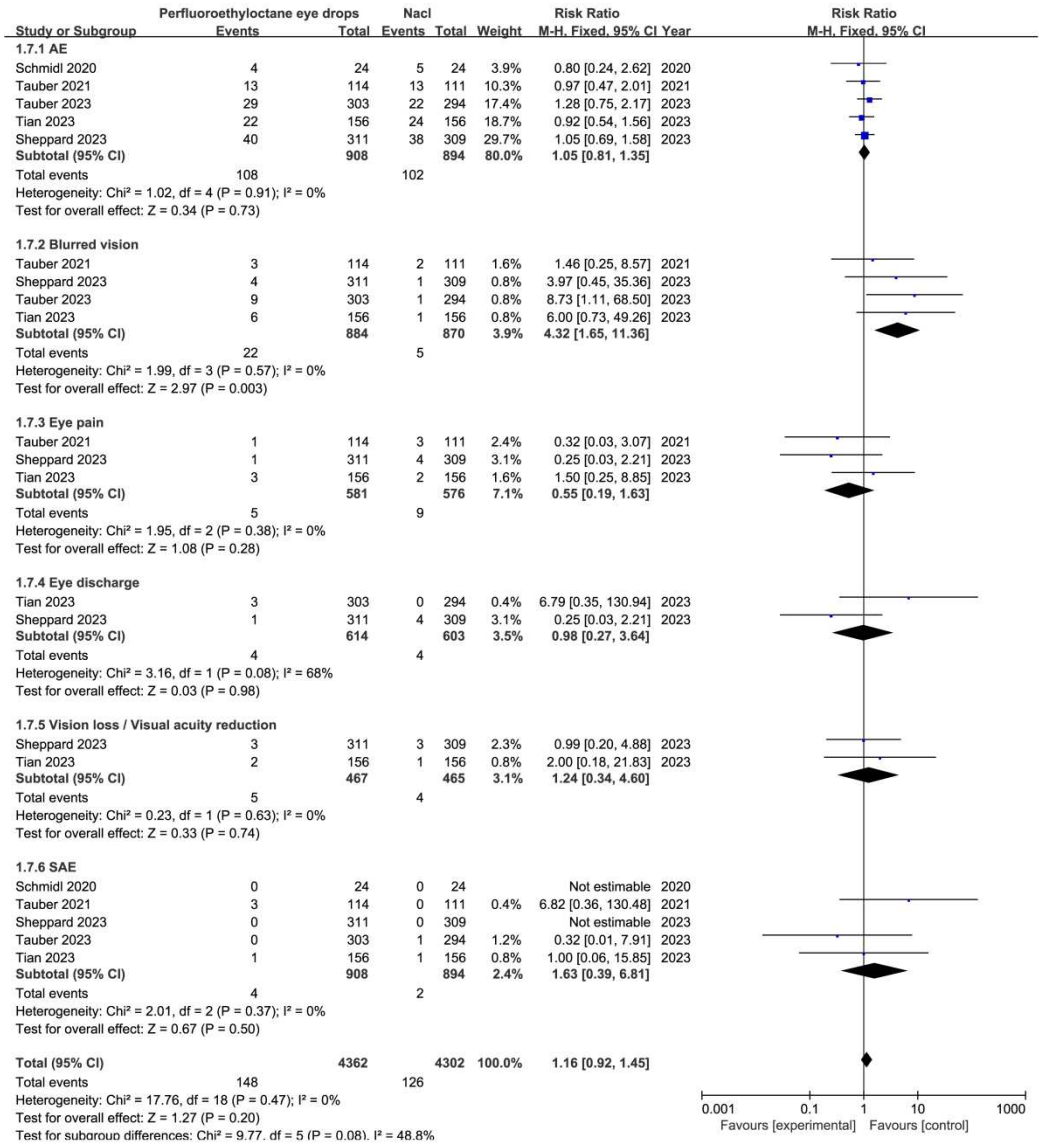
3.5 Safety Analysis

Five studies [13,15–18] reported adverse event data. The overall adverse event rate did not differ significantly between the perfluorohexyloctane and control groups (RR = 1.05, 95% CI: 0.81 to 1.35, P = 0.91, I^2 = 0%) (Figure 6).

In subgroup analyses of common ocular adverse events (Figure 6), blurred vision was significantly more frequent in the perfluorohexyloctane group (RR = 4.32, 95% CI: 1.65 to 11.36, P = 0.003, I^2 = 0%). Four studies reported this event (22/884 in the intervention group vs. 5/870 in the control group). All reported cases were mild and transient, typically resolving within minutes. No patient discontinued treatment due to blurred vision. The absolute risk increase was approximately 1.9%.

Eye pain (RR = 0.55, 95% CI: 0.19 to 1.63, P = 0.28, I^2 = 0%), eye discharge (RR = 0.98, 95% CI: 0.27 to 3.64, P = 0.98, I^2 = 68%), and visual acuity reduction (RR = 1.24, 95% CI: 0.34 to 4.60, P = 0.74, I^2 = 0%) did not differ significantly between groups.

Serious adverse events were rare (4/908, 0.44% in the intervention group; 2/894, 0.22%



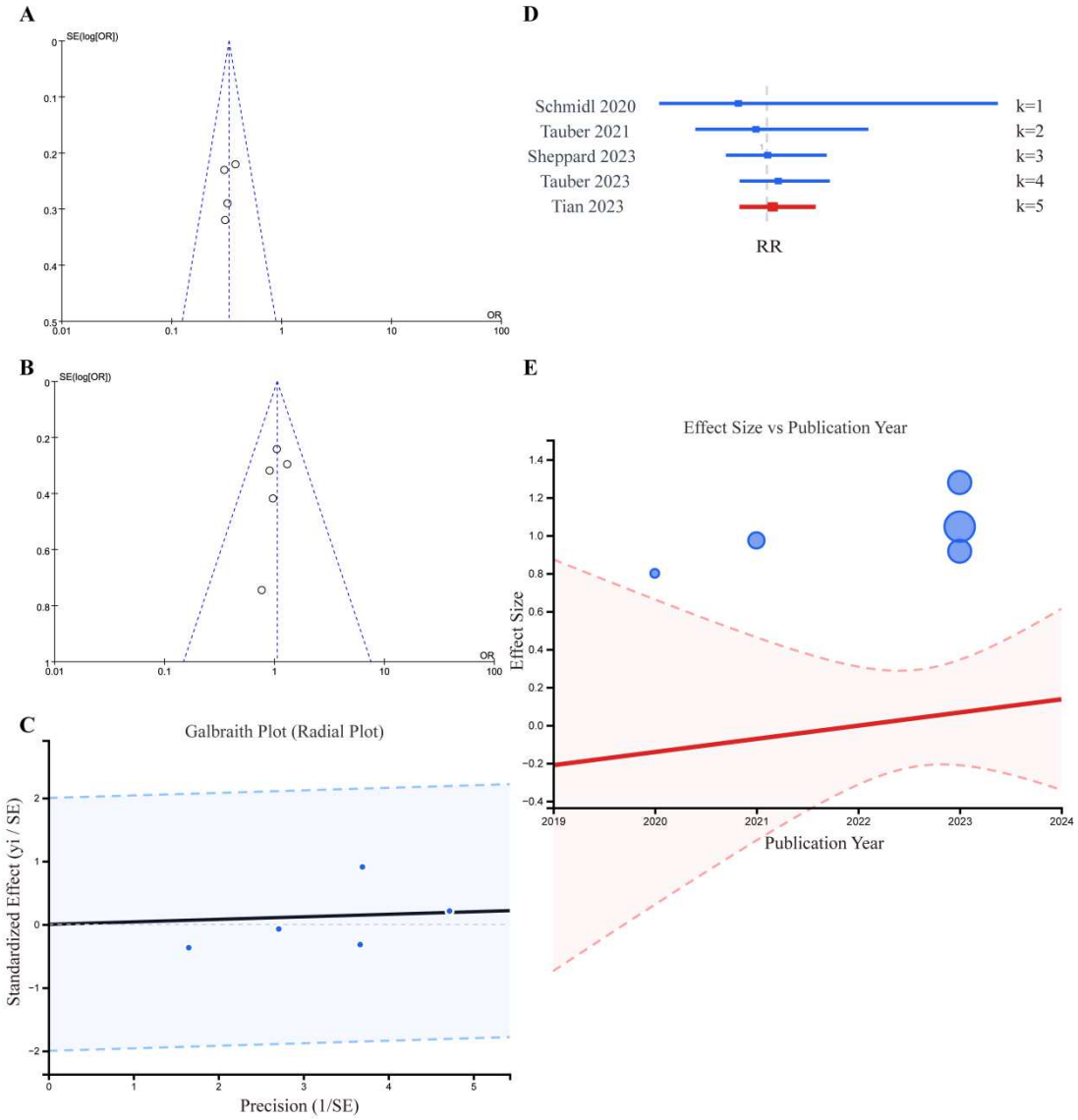
in the control group). None was related to perfluorohexyloctane. We did not perform a meta-analysis for serious adverse events due to the small number of events. We report them descriptively.

Figure 6. Forest plots of safety outcomes. (a) Overall adverse events; (b) Subgroup analysis of common ocular adverse events (blurred vision, eye pain, eye discharge, visual acuity reduction). AE, adverse event; RR, risk ratio; CI, confidence interval; M-H, Mantel-Haenszel; QID, four times daily. Overall AEs were reported in 5 studies (n = 1,802), with no significant difference between groups (RR = 1.05, 95% CI: 0.81 to 1.35, P = 0.91, I^2 = 0%). Blurred vision was significantly more frequent in the perfluorohexyloctane group (RR = 4.32, 95% CI: 1.65 to 11.36, P = 0.003, I^2 = 0%), though all events were mild and transient. A random-effects model was applied for eye discharge (I^2 = 68%).

3.6 Publication Bias

We generated funnel plots for tCFS (4 studies) and total adverse events (5 studies) (Figures 7A and 7B). The plots were generally symmetrical, suggesting a low risk of publication bias. Egger's test was not performed because fewer than 10 studies were included.

We also generated a Galbraith radial plot to further assess heterogeneity and identify



potential outliers (Figure 7C). All studies fell within the z = ±2 boundaries, indicating no significant outliers. This finding was consistent with the funnel plots and further supported the robustness of the results.

Figure 7. Publication bias and sensitivity analyses. (a) Funnel plot for tCFS (4 studies); (b) Funnel plot for total adverse events (5 studies); (c) Galbraith radial plot for total adverse events; (d)

Cumulative meta-analysis of adverse events by publication year; (e) Meta-regression plot of adverse events with publication year as covariate. SE, standard error; RR, risk ratio; CI, confidence interval. Funnel plots showed generally symmetrical distribution. The Galbraith radial plot showed all studies falling within the z = ±2 boundaries. Cumulative meta-analysis showed that the pooled RR remained stable around 1.0 as studies were added chronologically. Meta-regression showed no significant association between publication year and effect size (coefficient = 0.0694, SE = 0.1488, P = 0.641).

3.7 Sensitivity Analyses

3.7.1 Influence Diagnostics and Leave-One-Out Analysis

We used the Viechtbauer and Cheung (2010) method [22] to assess the influence of individual studies on the pooled results. Hat values ranged from 0.046 to 0.375. Cook's D values were all below 0.225. DFFITS values were all below 0.474. Studentized residuals were all below 1 in absolute value. These values were all below the respective outlier thresholds, indicating that no single study unduly influenced the pooled results. Leave-one-out analyses showed that the pooled RR ranged from 0.98 to 1.08 after removing any single study. The 95% CIs always crossed 1.0, and I^2 remained 0%. These results further confirmed the robustness of the safety analysis (Table 3).

Table 3. Influence diagnostics and leave-one-out sensitivity analysis for adverse events

Study omitted	LOO RR (95% CI)	LOO I^2	Cook's D	Hat value	Studentized residual	DFFITS
None (original pooled)	1.04 (0.81, 1.34)	0%	—	—	—	—
Schmidl 2020	1.05 (0.81, 1.37)	0%	0.0095	0.046	-0.445	-0.098
Tauber 2021	1.05 (0.81, 1.37)	0%	0.0053	0.124	-0.193	-0.073

Study omitted	LOO RR (95% CI)	LOO I^2	Cook's D	Hat value	Studentized residual	DFFITS
Sheppard 2023	1.04 (0.78, 1.37)	0%	0.0005	0.375	0.028	0.022
Tauber 2023	0.98 (0.76, 1.26)	0%	0.2241	0.230	0.867	0.473
Tian 2023	1.08 (0.81, 1.44)	0%	0.0822	0.226	-0.530	-0.287

Abbreviations: LOO, leave-one-out; RR, risk ratio; CI, confidence interval. Cook's D > 0.800 or Hat value > 0.400 was considered influential (no study met this threshold). RRs were pooled using a random-effects model.

3.7.2 Cumulative Meta-Analysis

Cumulative meta-analysis (Table 4, Figure 7D) showed that the pooled RR remained stable around 1.0 as studies were added chronologically. The RR ranged from 0.80 (first study) to 1.04 (all five studies). The 95% CIs always crossed 1.0, and I^2 remained 0% at each cumulative step. This indicates that the conclusion of no significant increase in adverse events remained stable as evidence accumulated.

Table 4. Cumulative meta-analysis of adverse events by publication year

Study Added	k	RR [95% CI]	Heterogeneity	P
Schmidl (2020)	1	0.80 [0.24, 2.62]	I^2 = 0.0%	1.000
Tauber (2021)	2	0.92 [0.50, 1.71]	I^2 = 0.0%	0.800

Study Added	k	RR [95% CI]	Heterogeneity	P
Sheppard (2023)	3	1.01 [0.71, 1.42]	I^2 = 0.0%	0.973
Tauber (2023)	4	1.08 [0.81, 1.44]	I^2 = 0.0%	0.600
Tian (2023)	5	1.04 [0.81, 1.34]	I^2 = 0.0%	0.757

Abbreviations: k, number of studies; RR, risk ratio; CI, confidence interval. Studies were cumulatively added in chronological order of publication. RRs were pooled using a random-effects model (DerSimonian-Laird method).

3.7.3 Meta-Regression Analysis

We performed meta-regression with publication year as the covariate (Table 5, Figure 7E). The coefficient was 0.0694 (SE = 0.1488). The Z-value was 0.47 (P = 0.641). This indicates no significant association between publication year and effect size. The Q_model was 0.22 (P = 0.641), indicating that the model was not significant. The Q_residual was 0.80 (df = 3, P = 0.849), indicating no residual heterogeneity. The R^2 value was 21.4%, meaning that publication year explained about 21.4% of the between-study variance. However, because the overall heterogeneity was extremely low, the absolute meaning of this percentage is limited. These results further support the robustness of the safety findings.

Table 5. Meta-regression analysis of adverse events with publication year as covariate.

Covariate	year (k = 5)
Coefficient	0.0694 (SE = 0.1488)
Z	0.4666

P-value	0.641
Intercept	-140.4224
Q_model	0.22 (p = 0.641)
Q_residual	0.80 (df = 3, p = 0.849)
R^2 (proportion of heterogeneity explained)	21.4%

The covariate does not significantly moderate the effect size (P ⩾ 0.05).

3.8 GRADE Evidence Quality

We rated the quality of evidence using the GRADE system (Table 6). The evidence for tCFS change and eye dryness VAS change was rated as high (⊕⊕⊕⊕). OSDI change was rated as moderate (⊕⊕⊕◯) due to the limited number of studies (k = 3) and the relatively wide confidence intervals. Adverse events were rated as high (⊕⊕⊕⊕).

Table 6. GRADE evidence profile for key outcomes.

Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality	Importance
tCFS change at Week 8	4	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High	Critical
Eye dryness VAS	4	RC	Not	Not	Not	Not	Not	⊕⊕⊕⊕	Critical

change at Week 8		T	serious	serious	serious	serious	serious	High	
OSDI change at Week 8	3	RCT	Not serious	Not serious	Not serious	Serious *	Not serious	⊕⊕⊕◯ Moderate	Important
Adverse events (safety)	5	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High	Critical
tCFS responder rate	3	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High	Important
Eye dryness VAS responder rate	3	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High	Important

4 Discussion

4.1 Efficacy and Clinical Significance

This study systematically evaluated the efficacy and safety of perfluorohexyloctane eye drops for DED. We included five studies [13,15–18] with 1,913 patients. Meta-analysis showed that perfluorohexyloctane four times daily for 8 weeks significantly improved corneal epithelial damage (tCFS, MD = -1.11, $P < 0.00001$) and dry eye symptoms (eye dryness VAS, MD = -10.28, $P < 0.00001$; OSDI, MD = -5.49, $P < 0.0001$). The pooled tCFS effect size exceeded the minimal clinically important difference (MCID = 1.0) [30], indicating that the effect was not only statistically significant but also clinically meaningful.

Time-point subgroup analysis showed that the effect of perfluorohexyloctane began at Week 2 (MD = -0.59) and increased through Week 8 (MD = -1.11). This progressive improvement is consistent with its mechanism of action. A single drop rapidly spreads over the ocular surface and forms a protective layer. Repeated use over time stabilizes the tear film and promotes corneal epithelial repair [31,32]. Corneal regions (inferior and temporal) both showed significant improvement with similar effect sizes. This suggests that the drug acts across the entire ocular surface rather than at specific focal sites.

From a clinical perspective, DED signs and symptoms are often discordant. Demonstrating improvement in both signs and symptoms within a single trial is challenging [33]. The phase 3 trials included in this meta-analysis all met dual primary endpoints for signs (tCFS) and symptoms (eye dryness VAS). The meta-analysis further confirmed the robustness of these findings. The dual efficacy of perfluorohexyloctane on corneal epithelial repair and symptom relief makes it a promising treatment for DED.

In addition, the improvement in OSDI score (MD = -5.49) reflects improved quality of life [34]. Responder analyses further support the clinical value of perfluorohexyloctane. Approximately 50% of patients achieved a tCFS improvement of $\geqslant 3$ points. Approximately 60% of patients achieved an eye dryness VAS improvement of $\geqslant 30\%$. These findings suggest that most DED patients can derive clinically meaningful benefit from this treatment.

4.2 Mechanism of Action and Safety

The efficacy of perfluorohexyloctane can be understood through its unique mechanism of action. First, perfluorohexyloctane has very low surface tension. This allows it to spread rapidly over the ocular surface. Its amphiphilic nature enables it to form supramolecular structures at the lipid–air interface. This creates a stable tear film barrier that prevents excessive water evaporation [35,36]. Second, animal studies have shown that perfluorohexyloctane can penetrate the meibomian glands. It remains at high concentrations in the glands for up to 24 hours, potentially helping to restore their secretory function [37].

The mechanistic study by Schmidl 2020 directly supports this theoretical framework. After 4 weeks of treatment, tear film thickness (TFT) significantly increased from baseline (LS mean difference +6.42%, $P = 0.014$). Lipid layer thickness (LLT) also significantly increased (LS mean difference +16.34%, $P < 0.01$). These findings provide direct evidence that perfluorohexyloctane stabilizes the lipid layer and increases tear film thickness [14]. This also explains why perfluorohexyloctane effectively improves corneal epithelial damage and dry eye symptoms even though TFBUT was not significantly prolonged in our exploratory analysis. The core mechanism is stabilization of the tear film lipid layer and reduction of evaporation, rather than simply prolonging TFBUT [38,39].

In terms of safety, we found no significant difference in overall adverse event rates between perfluorohexyloctane and saline. The overall safety profile was favorable.

Blurred vision was the only adverse event that was significantly increased (RR = 4.32, P = 0.003). However, in all reported cases, blurred vision was mild and transient, typically resolving within minutes. No patient discontinued treatment due to blurred vision. The absolute risk increase was only about 1.9%. Other ocular adverse events such as eye pain, eye discharge, and visual acuity reduction did not differ significantly between groups. Serious adverse events were rare (0.44% in the intervention group vs. 0.22% in the control group). None was related to perfluorohexyloctane. This safety profile compares favorably with some existing DED treatments. For example, cyclosporine and lifitegrast eye drops have instillation site reaction rates of approximately 10% – 15% [40,41]. The favorable tolerability of perfluorohexyloctane may be related to its preservative-free formulation [42,43,44].

4.3 Comparison with Previous Meta-Analyses and Limitations

Previous meta-analyses on perfluorohexyloctane have uniformly reported significant benefits in tCFS reduction and symptom alleviation [45,46,47]. Compared with these studies, our work has several strengths. First, we included all available analyzable data, making the evidence base more complete and the population coverage broader. Second, we performed time-point subgroup analyses and corneal region subgroup analyses for the first time. These analyses revealed the time–effect trend of perfluorohexyloctane and its pan-ocular surface coverage. Third, we supplemented the analysis with influence diagnostics, cumulative meta-analysis, and meta-regression, which comprehensively validated the robustness of the results. Finally, our OSDI analysis showed that perfluorohexyloctane significantly improved patient quality of life (MD = -5.49), providing new evidence for a positive outcome that was not observed in previous meta-analyses.

This study has several limitations. Several limitations warrant consideration. The observation period across studies was short (4–8 weeks), and data beyond 12 months are not yet available [48]. Additionally, the control arms of two large US trials (Tauber 2023 and Sheppard 2023) employed BAK-preserved saline (0.01% benzalkonium chloride), which may have influenced the performance of the comparator group [49]. Third, all included studies excluded patients with severe DED (tCFS > 11), contact lens wearers, and those with secondary DED. This limits the generalizability of the results. Fourth, TFBUT could not be reliably meta-analyzed because only two studies reported it and one provided only estimated data. Fifth, the number of included studies was small (only five). Some subgroup analyses (e.g., Week 4 time point) included only two studies, making the I^2 estimates unstable. These

results should therefore be interpreted cautiously. Future studies with longer follow-up (⩾12 months) and broader patient populations are needed to further validate the efficacy and safety of perfluorohexyloctane [50,51,52].

5 Conclusions

Perfluorohexyloctane eye drops (four times daily) effectively reduce corneal epithelial damage and dry eye symptoms in patients with DED. The effect begins at Week 2 and increases through Week 8. The overall safety profile is favorable. Blurred vision is the most common transient adverse event, but it is mild and self-limiting and does not affect treatment continuity. The available evidence supports perfluorohexyloctane as an effective treatment option for DED.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests. The sponsors of the original studies (Jiangsu Hengrui Pharmaceutical Co., Ltd. and Bausch + Lomb) participated in the design, conduct, data collection, analysis, and interpretation of their respective studies. The authors of this systematic review received no direct funding from any pharmaceutical company for the conduct of this study, and no pharmaceutical company had any role in the study design, data extraction, analysis, interpretation, or writing of this manuscript. Zuojun Gao, Sonja Krösser, and Yunxia Zhang were employees of Jiangsu Hengrui Pharmaceutical Co., Ltd. or Novaliq GmbH during the conduct of the original studies but were not involved in the current systematic review.

Clinical trial number: not applicable.

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Author Contributions

Xiaolong Zhang: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft. Huimei Chen: Conceptualization, Methodology, Writing – review & editing. Canming Xie: Investigation, Visualization. Qinghua Peng: Supervision. Jian Shi: Project administration, Supervision, Writing – review & editing. Xiaolei Yao: Funding acquisition, Resources, Project administration, Supervision, Writing – review & editing.

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