Title

Perfluorohexyloctane in Dry Eye Disease: A Systematic Review of its Efficacy and Safety as a Novel Therapeutic Agent

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Abstract

Perfluorohexyloctane (F6H8), a physically and chemically inert synthetic compound, has recently emerged as a promising candidate for the treatment of DED due to its unique properties. A systematic review that only include full-length randomized controlled studies (RCTs), reporting the effects of F6H8 in three databases, PubMed, Scopus and Web of Science, was performed according to the PRISMA statement. The search period was performed between June 1, 2023, and June 21, 2023. The Cochrane risk of bias tool was used to analyze the quality of the studies selected. A total of six RCTs were included in this systematic review. F6H8 tear substitutes treatment achieved a higher improvement than control group interventions in most of the reported variables. The mean differences between both groups were in favor of F6H8 and were as follow: eye dryness score (EDS) base on a visual analogue scale (VAS) of -6.12 ± 4.3 points, ocular surface disease index (OSDI) questionnaire score of -2.8 ± 2.3 points, lipid layer thickness (LLT) of 11.4 ± 10.4 μm, total corneal fluorescein staining (tCFS) of -0.8 ± 0.3 points and ocular treatment-emergent adverse events (TEAEs) of -0.66 ± 1.7. Tear film break-up time (TBUT) was the only variable in favor of control group with a mean of -0.5 ± 0.4 s. Patient satisfaction after F6H8 tear substitutes treatment was high. Therefore, F6H8 tear substitutes improve dry eye symptoms and signs with a satisfactory tolerability and could be recommended in patients with DED.

KEYWORDS

perfluorohexyloctane; tear substitutes; dry eye disease; meibomian gland dysfunction.

1. Introduction

Dry eye disease (DED) is a prevalent ocular disease characterized by symptoms such as ocular discomfort, visual disturbances, and tear film instability [1]. It affects a substantial proportion of the population and presents significant challenges in terms of diagnosis and management [2]. Despite the availability of various treatment options, there is a need for more effective therapeutic agents to ameliorate symptoms and improve the quality of life of patients with DED [3]. The multifactorial nature of DED presents complexities in its treatment [4]. The underlying causes can include tear deficiency, excessive tear evaporation, or a combination of both [5]. In addition, DED may coexist with conditions such as meibomian gland dysfunction (MGD) or autoimmune diseases, complicating management strategies [5–7]. These challenges suggest the need for novel therapeutic agents that target specific mechanisms involved in the pathogenesis of DED [5,7,8].

Perfluorohexyloctane (F6H8) has emerged as a promising candidate for the treatment of DED [9,10]. F6H8 is a physically and chemically inert synthetic compound that has unique properties that make it suitable for ocular applications [11]. Its excellent biocompatibility [12–14], low surface tension [11,15], and high lipid affinity [14] make it a potential therapeutic agent capable of addressing tear film instability and improving ocular surface health in patients with DED [16]. F6H8 has been on the market since 2015 as an approved medical device in Europe, Australia, and New Zealand, and gained FDA approval as a drug for use in the United States in 2023. The assessment of F6H8 efficacy and safety in DED is of paramount significance [17]. By evaluating its therapeutic effects, as well as adverse events and tolerability, it is possible to determine its potential benefits and clinical relevance [18,19]

To date some published studies have evaluated the effects of F6H8 tear substitutes in DED [9–14,18–20]. However, to the best of our knowledge, no systematic reviews have

explored the available literature regarding the benefits of F6H8 tear substitutes treatment. Therefore, the objective of this systematic review is to evaluate the efficacy and safety of F6H8 tear substitutes in the management of DED based on the available randomized controlled trials (RCTs) Through this review, we aim to provide a comprehensive overview of the current evidence on F6H8, enabling evidence-based decision making and guiding future research directions.

2. Method of Literature Search

2.1 Data sources and search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21,22]. We identified 56 articles published before June 21, 2023, through the following databases: PubMed, Scopus and Web of science. The data search strategy with Boolean operators was as follows: (perfluorohexyloctane OR NOV03 OR F6H8 eye drops) AND (dry eye disease OR DED OR evaporative dry eye OR EDE OR aqueous-deficient dry eye OR ADDE OR meibomian gland dysfunction OR MGD). The references of the retrieved articles were reviewed to identify other related studies if they met the inclusion criteria.

2.2 Study selection

All those 56 articles identified through the search strategy were considered and analyzed. Duplicate studies were removed by DistillerSR software (DistillerSR Inc., Ottawa, Canada) [23]. The remaining studies underwent additional screening stages, which included title screening, abstract screening, and full-text screening. Studies unrelated to the topic were excluded from the review during title and abstract screening. Full-text screening studies that did not include F6H8 tear substitutes treatment was also excluded from the review. These studies were reviewed by two investigators (ABS and JMSG) who selected them according to the inclusion and exclusion criteria. The inclusion criteria were

as follows: human studies, full-length original articles and prospective randomized controlled studies. The exclusion criteria included non-English publications and unindexed journals. There were no restrictions placed on the country in which the study was performed, the follow-up period, the sample size or results of the studies.

2.3 Quality assessment and data extraction

The data from each study were collected and summarized independently in tables designed by two researchers (ABS and JMSG). The following information was obtained from each article: (1) author and date of publication (year), (2) study design, (3) mean follow-up of all patients in the whole procedure (expressed in months), (4) number of patients, (5) mean age of the patients (expressed in years), (6) patient sex (male/female), (7) number of eyes involved, (8) study group intervention, (9) control group intervention, (10) F6H8 posology and (11) conflicts of interest.

Regarding the results of the studies, the following date were collected: (12) eye dryness score based on a visual analog scale (EDS, values from 0 to 100) [24], (13) ocular surface disease index (OSDI, values from 0 to 100) [25]; (14) tear break-up time (TBUT, expressed in seconds, s); (15) lipid layer thickness (LLT, expressed in micron, μm); (16) Schirmer test (ST, expressed in millimeters, mm]; (17) total corneal fluorescein staining (tCFS), which tCFS was defined as the sum of fluorescein staining in 5 areas (inferior, superior, central, nasal and temporal) with a maximum score of 15 points [20]. Fluorescein staining in each area was assessed with the National Eye Institute scale from grade 0 (no staining) to grade 3 (heavy staining) [26]; (18) meiboscore, which was defined as the sum of meibomian gland expression in 5 central meibomian glands on the lower eyelid with a maximum score of 15 points [27]. Meibomian gland expression was grade from 0 to 3, where grade 0 is normal meibum, grade 1 is turbid oil meibum, grade 2 is turbid and viscous oil appearance meibum and grade 3 is toothpaste-like consistency

meibum or no expression [18]; (19) ocular treatment-emergent adverse events (TEAEs) (expressed as percentages); (20) patient satisfaction ranging from 0 (no acceptance) to 10 (high acceptance) and finally (21) authors judgment expressed by commenting in favor or against of F6H8 tear substitutes treatment. Data synthesis was performed according to the Cochrane guideline for synthesis without meta-analysis (SWiM) [28]. Baseline and last visit values for all these variables were collected in the treatment (T) and control (C) groups. Intra-group clinical outcomes were defined as "Last visit (LV) – Baseline (B) differences". Inter-group clinical outcomes were defined as "T group $_{(LV-B)}$ – C group $_{(LV-B)}$ differences". Mean ± SD for each variable were calculated to report intra-group and inter-group clinical outcomes.

The literature that remained after full-text screening was examined to assess the quality of the studies. To avoid the risk of bias, two dependable authors created a synopsis based on the Cochrane risk of bias tool [29], which includes the following items: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other sources of bias. A third nonblinded assessor decided the quality of the studies when disagreements occurred between the two assessors.

3. Results

3.1 Study characteristics

The study selection process of this systematic review is presented with a flowchart diagram in Fig. 1. The design of the included studies was prospective randomized controlled trials published between 2020 and 2023. This systematic review included 1965 eyes from 1965 patients with a mean age of 46.4 ± 16.1 years. The sex distribution was 1477 females (75.1%) and 488 males (24.9%). Patient follow-up, expressed in months, ranged from 1 month [12] to 3 months [19], with a mean follow-up of 2 ± 0.6 months.

Regarding study group intervention, 4 studies used NOV03 (Novaliq GmbH, Heidelberg, Germany) [13,14,18,20], 1 study used NovaTears (Novaliq GmbH, Heidelberg, Germany) [12] and 1 study used EvoTears (Ursapharm GmbH, Saarbrücken, Germany) [19]. Across the studies, various brand names such as NOV03, NovaTears, and EvoTears were used. However, it should be noted that all these formulations are based on the active ingredient F6H8. Different interventions were used in the control group, such as saline solution (sodium chloride, NaCl 0.6% or 0.9%) [12–14,18,20], and cationic emulsion (mineral oils, MOs 0.5%) [19]. Five studies had conflicts of interest by the authors (supported by Novaliq GmbH, Heidelberg, Germany) [12–14,18,20]. More detailed study characteristics and tear substitutes composition are presented in Table 1.

3.2 Outcomes

Regarding efficacy outcomes, 5 studies reported dry eye symptom outcomes [12–14,18,20], of which 3 studies used the OSDI questionnaire [12,14,18], while all studies used the EDS [12–14,18,20]. All studies also reported dry eye sign outcomes, of which 3 studies evaluated TBUT [12,14,18], 2 studies assessed LLT [12,19], 5 studies evaluated tCFS [12–14,18,20] and 1 study assessed ST and meiboscore [14]. Regarding safety outcomes, 5 studies reported ocular TEAEs [12–14,18,20], while patient satisfaction was reported by 1 study [14].

Intra-group clinical outcomes are presented in Tables 2 and 3. Regarding treatment group, most of the outcomes achieved an improvement, with a mean EDS of -24 ± 10.3 points, mean OSDI questionnaire score of -14.9 ± 10.9 points, mean TBUT of 3.6 ± 1,6 s, mean LLT of 16.7 ± 4.2 μm and mean tCFS of -2.1 ± 0.9 points. The meiboscore also achieved an improvement of -2.1 points, while ST showed a worsening of -1 mm. Regarding control group, most of the outcomes also achieved an improvement, with a mean EDS of -17.9 ± 6.4 points, mean OSDI questionnaire score of -12.2 ± 8.7 points, mean TBUT of

4.2 ± 2.1 s, mean LLT of 5.4 ± 6.3 μm and mean tCFS of -1.3 ± 0.7 points. The ST and meiboscore also achieved an improvement of 0.3 mm and -1.8 points, respectively.

Inter-group clinical outcomes are presented in Table 4. Most of the outcomes were in favor of the treatment group, with a mean EDS of -6.12 ± 4.3 points, mean OSDI questionnaire score of -2.8 ± 2.3 points, mean LLT of 11.4 ± 10.4 μm and mean tCFS of -0.8 ± 0.3 points. The meiboscore also achieved a treatment group improvement of -0.3 points compared to the control group. However, TBUT and ST were in favor of control group with a mean of -0.5 ± 0.4 s and -1.3 mm, respectively. Regarding adverse events, the treatment group reported that ocular TEAEs was 0.66 ± 1.7 % lower than the control group. In addition, patient satisfaction was 0.9 points higher in the treatment group compared to the control group.

3.3 Risk of bias

The risk of bias summary of the included studies is presented in Fig. 2. Risk of bias assessment was classified into three evidence level groups: (1) studies with a low risk of bias (Tauber et al. (2021) [18], Tauber et al. (2023) [20], Sheppard et al. [13] and Tian et al. [14]), (2) studies with an unclear risk of bias (Schmidl et al. [12] and Habbe et al. [19]) and (3) studies with a high risk of bias (no studies). The overall risk of bias summary of the domains used in each study is presented in Fig. 3. The items used to assess the risk of bias showed an overall low risk of bias, which was of 68%. Therefore, no study was excluded due to risk of bias. The Robvis tool (NIHR, Bristol, UK) was used to create risk of bias assessment figures [30].

4. Discussion

Tear film hyperosmolarity is considered the trigger for the ocular surface inflammatory mechanism resulting in the dry eye symptoms and signs [5,31,32]. Tear substitutes are

usually the first line of treatment for patients with DED [3,33]. Therefore, new formulations that improve the tear film stability and restore the homeostasis of the ocular surface are under research [33,34]. This systematic review aimed to report the efficacy and safety of F6H8 tear substitutes as a novel therapeutic agent for patients with DED.

4.1 Non-randomized clinical trials on Perfluorohexyloctane

Since F6H8 has been approved as a medical device in Europe, Australia, New Zealand and the United States, several studies have evaluated the mechanism through which F6H8 could improve therapeutic outcomes in DED [11,35–37]. Stolowich et al. [35] reported a significant oxygen content within F6H8, which may be delivered to the ocular surface to facilitate corneal healing in patients with DED. In parallel in-vitro studies, Vittitow et al. [36] and Borchman et al. [37] reported that F6H8 significantly reduced the evaporation rate of the tear film. In addition, Agarwal et al. [11] achieved similar findings, demonstrating the ability of F6H8 to significantly enhance the LLT in rabbits. These results suggest the potential of F6H8 to stabilize the tear film lipid layer and thus ameliorate DED symptoms and signs.

Regarding studies in humans, Steven et al. [9,10] and Jacobi et al. [38] evaluated the effects of F6H8 administered 4 times daily on DED symptoms and signs after 8 weeks of follow-up. Both studies reported that F6H8 significantly improved OSDI score, TBUT, tCFS, as well as meibomian glands function in patients with DED. Similar results in tCFS were obtained by Orobia et al. [39] after 6 weeks of follow-up, who also reported that 57.4 % of compliant patients reported feeling better compared to the 12.5 % of non-compliant patients. In addition, Eberwein et al. [40] analyzed the effects of F6H8 for the treatment of DED in patients with ocular graft-versus-host disease, reporting that 57% of patients showed relief from DED symptoms after 12 weeks of follow-up. Overall, these

clinical trials suggest that F6H8 may be a promising option for the treatment of DED, but RCTs are needed.

4.2 Randomized controlled trials on Perfluorohexyloctane

4.2.1 Perfluorohexyloctane efficacy

Schmidl et al. [12], Tauber et al. (2021) [18], Tauber et al. (2023) [20], Sheppard et al. [13] and Tian et al. [14] assessed dry eye symptoms by EDS. This questionnaire is based on a visual analog scale that quantifies both the severity and frequency of dry eye symptoms and it is significant correlated with OSDI score [41,42]. Schmidl et al. [12], Tauber et al. (2021) [18], Tauber et al. (2023) [20], Sheppard et al. [13] and Tian et al. [14] reported that patients who received F6H8 tear substitutes treatment achieved an EDS improvement of -6.1 ± 4.3 points compared to the NaCl solution. The significant improvements in EDS reported by Sheppard et al. [13], Tauber et al. (2023) [20] and Tian et al. [14] were substantially higher than those reported by Schmidl et al. [12] and Tauber et al. (2021) [18] in the F6H8 group. It is well-known that dry eye severity increases with age [2,43]. In fact, Sheppard et al. [13], Tauber et al. (2023) [20] and Tian et al. [14] included patients 7.6 ± 1.4 years older compared to Schmidl et al. [12] and Tauber et al. (2021) [18], which may explain these results. Dry eye symptoms were also assessed with the OSDI questionnaire. This questionnaire is the most widely used for DED studies and it is validated in different languages [44–47]. Similar results were reported by Schmidl et al. [12], Tauber et al. (2021) [18] and Tian et al [14] in the F6H8 group with an OSDI score improvement of -2.8 ± 2.2 points compared to the NaCl solution group. The control group also showed improvements in EDS and OSDI score, which may be due to NaCl solution instillation. This compound has shown to be essential in the maintenance of the cornea epithelial surface, improving dry eye symptoms and signs [3,48].

Regarding tear film stability, Schmidl et al. [12], Habbe et al. [19] and Tian et al. [14] reported similar TBUT improvements in both groups. However, Schmidl et al. [12] and Habbe et al. [19] reported that patients who received F6H8 tear substitutes treatment achieved an LLT improvement of 11.4 ± 10.4 μm compared to the MOs solution. In addition, Tian et al. [14] also evaluated TS, but it remained unchanged in both groups. It is important to mention that this study performed ST without anesthesia, therefore the results are no reliable due to the action of reflex tearing [6]. Regarding ocular surface health, Schmidl et al. [12], Tauber et al. (2021) [18], Tauber et al. (2023) [20], Sheppard et al. [13] and Tian et al. [14] reported that patients who received F6H8 tear substitutes treatment achieved a tCFS reduction of -0.84 ± 0.3 points compared to the NaCl solution. These clinical effects on TBUT, LLT and tCFS may be explained by two properties of F6H8. First, its low surface tension allows to enhance the tear film spreading [11,15], and second its amphiphilic nature promotes the formation of new molecular structures at the lipid-air interface [49,50]. Both properties may help to restore tear film stability and prevent its evaporation [11–14,18,20], which facilitates rapid corneal healing [11,13]. This theoretical concept is consistent with the recent results reported by Borchman et al. [37] who demonstrated that F6H8 reduced the evaporation rate by 80% in an in-vitro study.

Regarding MGD, Tian et al. [14] was the only study that analyzed meibomian glands reporting that patients who received F6H8 tear substitutes treatment achieved a meiboscore improvement of -0.3 points compared to the NaCl solution. In a recent study, Kroesser et al. [51] also reported that the highest F6H8 concentration were found in the tear film and meibomian glands after carbon 14-labeled F6H8 tear substitute instillation in rabbits. In addition, Steven et al. [10] also reported that F6H8 tear substitutes treatment significantly improved meibomian glands function in patients with DED. Therefore, it is

possible that F6H8 may penetrate the meibomian glands, interact with lipids inside the gland and thus improve secretory function [14,18,20,52], which would be consistent with increased LLT as reported by Schmidl et al. [12] and Habbe et al. [19]

4.2.2 Perfluorohexyloctane safety

Schmidl et al.[12], Tauber et al. (2021) [18], Tauber et al. (2023) [20], Sheppard et al. [13] and Tian et al. [14] reported ocular TEAEs after F6H8 tear substitutes treatment**.** Overall, Patients who received F6H8 tear substitutes treatment reported 0.66 ± 1.7 % fewer ocular TEAEs compared to NaCl solution. In addition, Tian et al. [14] was the only study to report patient satisfaction showing that F6H8 tear substitutes achieved higher acceptance compared to NaCl solution. This is probably due to the F6H8 eye drops are preservative-free, while the NaCl solution used in the control groups was preserved with benzalkonium chloride (BAK). The effects of BAK on ocular tissue cells is well-known [53,54]. Chronic exposure to BAK elevates concentrations of inflammatory markers in ocular tissues [55], leading to corneal epithelium and conjunctival goblet cells apoptosis [56–58]. In addition, this BAK-induced cytotoxic effect on the ocular surface promotes clinical manifestations such as conjunctival and corneal epithelial surface staining [59], which results in ocular discomfort including foreign body sensation, stinging and burning [60].

4.3 Strengths and limitations

The main strength of this systematic review is the results obtained due to all studies included were RCTs with an overall low risk of bias. In addition, the interventions in both groups, as well as the eye drops doses applied per day were practically the same between the studies. However, since the included studies were limited and they differed in dry eye criteria, number of patients included and demographic characteristics, a meta-analysis

was not performed. This study has some limitations that need to be addressed. First, the relatively short follow-up period of the studies included. Therefore, larger, well-designed, strictly blinded, multicenter RCTs with extensive follow-up evaluating the effect of F6H8 on tear film and MGD are needed. In fact, the 12-month Kalahari trial is ongoing in the US[61], which will provide additional information regarding the safety and efficacy of F6H8 tear substitutes treatment in long term use. Second, the control groups received BAK-preserved saline, which is not considered the standard treatment for dry eye disease [62]. This may give an advantage to the evaluation of the F6H8 tear substitutes effectiveness, which are preservative-free. Therefore, RCTs comparing the safety and efficacy of F6H8 tear substitutes with other preservative-free tear substitutes are also needed. Finally, it is important to mention that Habbe et al. [19] was the only study that did not use saline solution as a control and reported no conflict of interest. The remained studies included in this systematic review were supported by Novaliq GmbH, thus further non-industry funded research would be interesting to ensure the fairness and integrity of the results.

5. Conclusion

In conclusion, this systematic review has demonstrated that F6H8 tear substitutes treatment achieves better results than NaCl solution, reporting high patient satisfaction with minimal TEAEs. F6H8 tear substitutes improve DED symptoms and signs such as OSDI score, TBUT, LLT and tCFS. Therefore, F6H8 tear substitutes seem to be an effective and safe treatment that should be recommended for patients with DED. In addition, F6H8 is among major tear substitute candidates for MGD treatment, but further RCTs are needed.

Declaration of competing interest

The authors have no financial/non-financial competing interest.

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Figure legends

Fig. 1. Flowchart study selection process according to the PRISMA statement.

Fig. 2. Risk of bias summary of the included studies with traffic light plot. The traffic lights represent the author's risk of bias judgment in each domain (D) used to assess the quality of the studies.

Fig. 3. Overall risk of bias summary of the domains with bar plot. Bars represent the overall author's risk of bias judgment in each domain presented as percentages.

Figure 1

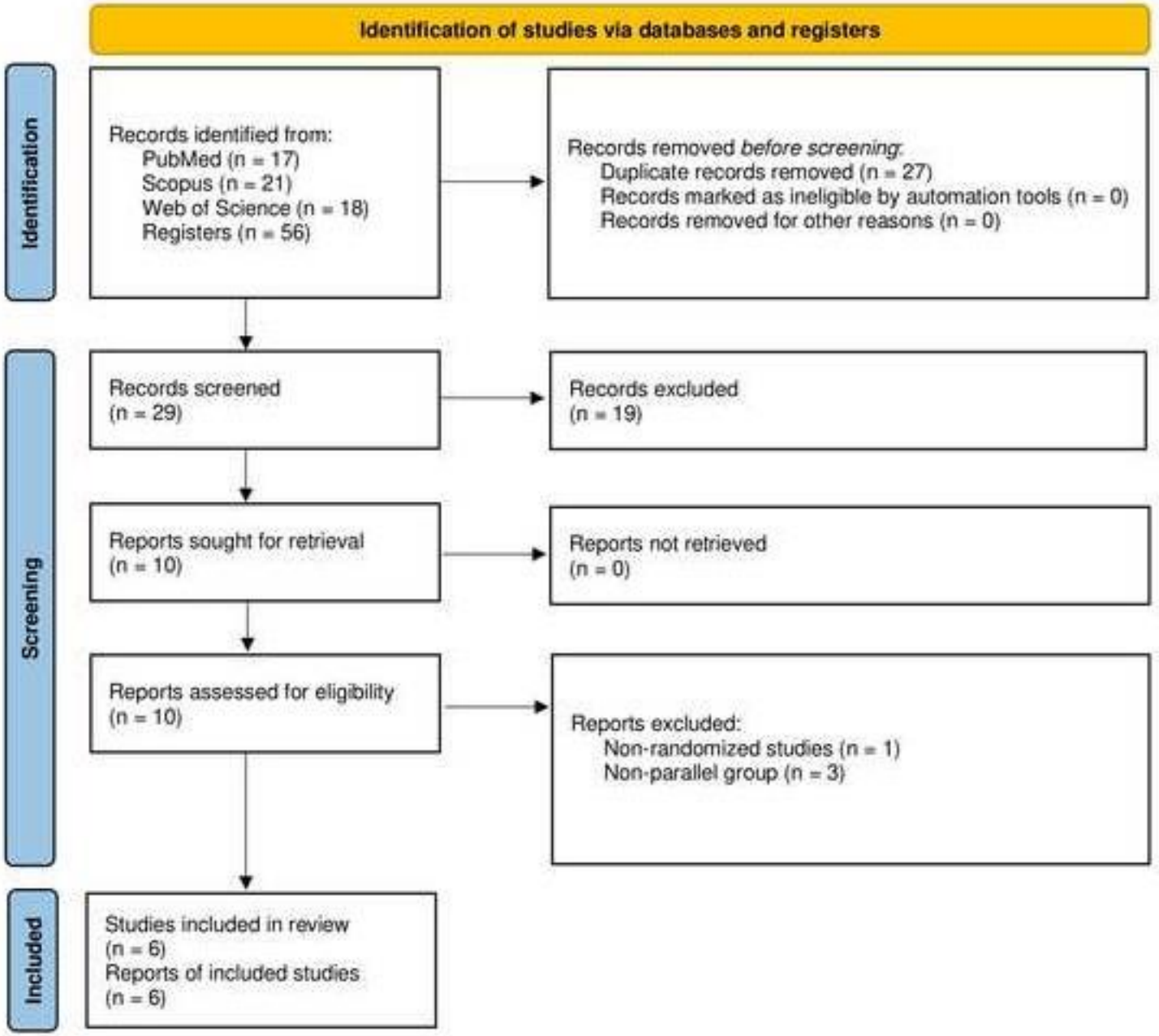

Figure 2

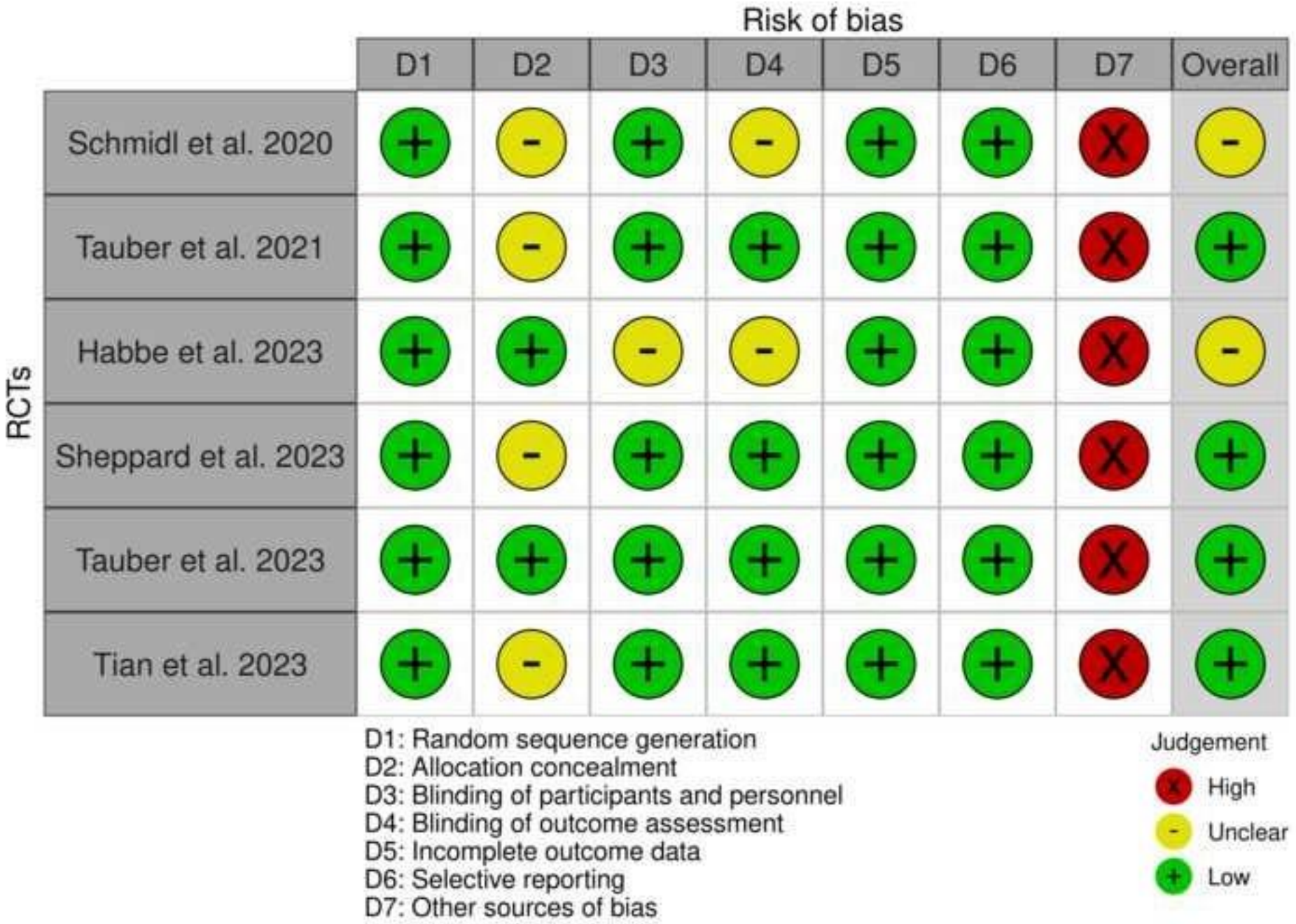

Figure 3

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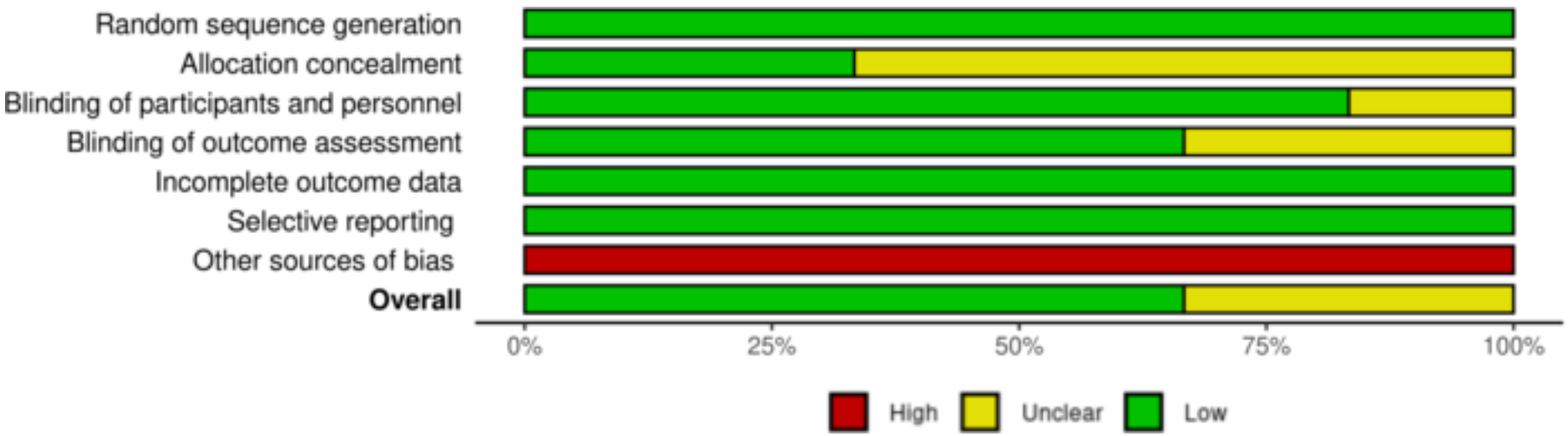

Table 1
Summary of included RCTs.

Author (date)	Design	F/U[a]	Patients (TG/CG)	Age[b] (TG/CG)	Sex (F/M)	Eyes	Inclusion criteria	Intervention	Control	Posology[c]	CoI
Schmidl et al. [12] 2020	MN SM	1	48 (24/24)	37.5 ± 12.5 (NR)	36/12	48	DED MGD	NovaTears (100% Perfluorohexyloctane)	Saline solution (NaCL 0.9%)	6	Yes
Tauber et al. [18] 2021	MT DM	2	336 (225/111)	53.6 ± 19.9 (53.5 ± 22.9 / 53.8 ± 19.9)	243/93	336	DED MGD	NOV03 (100% Perfluorohexyloctane)	Saline solution (NaCL 0.9%)	6	Yes
Habbe et al. [19] 2023	MN	3	52 (18/34)	28 ± 12.8 (24.2 ± 4.1 / 30.5 ± 11.1)	32/20	52	DED MGD	EvoTears (100% Perfluorohexyloctane)	Cationic emulsion (MOs 0.5%)	8	No
Sheppard et al. [13] 2023	MT DM	2	620 (311/309)	53.5 ± 20.3 (53.3 ± 19.8 / 53.8 ± 20.8)	488/132	620	DED MGD	NOV03 (100% Perfluorohexyloctane)	Saline solution (NaCL 0.6%)	6	Yes
Tauber et al. [20] 2023	MT DM	2	597 (303/294)	61 [19-88] (60.3 [20-87] / 61.6 [19-88])	433/164	597	DED MGD	NOV03 (100% Perfluorohexyloctane)	Saline solution (NaCL 0.6%)	6	Yes
Tian et al. [14] 2023	MT DM	2	312 (156/156)	44.6 ± 15.2 (45.4 ± 15.2 / 43.7 ± 15.1)	245/67	312	DED MGD	NOV03 (100% Perfluorohexyloctane)	Saline solution (NaCL 0.6%)	6	Yes

CG, Control group; CoI, Conflict of interest; DM, Double-masked; DED; Dry eye disease; F, Female; F/U, Follow-up; M, Male; MN, Monocentric; Mos, Mineral oils; MT, Multicenter; MGD, Meibomian gland dysfunction; NaCl, Sodium chloride; NR, Not reported; RCTs, Randomized controlled trials; SM, Single-masked; TG, Treatment group;

[a] Expressed as months.

[b] Expressed as mean ± SD or median [IQR], years.

[c] Eye drops dose in both eyes expressed as hours per day.

Table 2
Baseline, Last visit and Differences (Last visit - Baseline) outcomes in the treatment group.

Author (Date)	Assessment	EDS (0-100)	OSDI (0-100)	TBUT, s	LLT, µm	ST, mm	tCFS (0-15)	Meiboscore (0-15)	Ocular TEAEs, %	Satisfaction (0-10)
Schmidl et al. [12] 2020	Baseline	35 ± 15	44 ± 22	8.5 ± 4.4	76.5 ± 15.7	NR	4.1 ± 1,4	NR	-	-
	Last visit	22.2 ± 17.3	33.4 ± 21.6	13.6 ± 5.3	89 ± 16.4	NR	2.8 ± 1.6	NR	16.7	NR
	Difference $_{LV-B}$	**-12.8**	**-10.6**	**5.1***	**12.5**	-	**-1.3**	-	-	-
Tauber et al. [18] 2021	Baseline	68.6 ± 21.8	55.3 ± 17.4	3 ± 0.9	NR	14.6 ± 8.9	7 ± 2.2	7.6 ± 3.5	-	-
	Last visit	56.8 ± 18.7	51 ± 9.2	NR	NR	NR	5.8 ± 1.8	NR	11.4	NR
	Difference $_{LV-B}$	**- 11.8***	**-4.3**	-	-	-	**-1.2***	-	-	-
Habbe et al. [19] 2023	Baseline	NR	NR	12.4 ± 5.9	45.8 ± 8.7	NR	NR	NR	-	-
	Last visit	NR	NR	16.9 ± 4.7	66.7 ± 19.5	NR	NR	NR	NR	NR
	Difference $_{LV-B}$	-	-	**4.5***	**20.9***	-	-	-	-	-
Sheppard et al. [13] 2023	Baseline	64.7 ± 19.5	55.2 ± 17.4	3.2 ± 0.9	NR	12.7 ± 7.5	7 ± 2	7.9 ± 3.5	-	-
	Last visit	35.2 ± 15.5	NR	NR	NR	NR	4.7 ± 1.6	NR	12.9	NR
	Difference $_{LV-B}$	**-29.5***	-	-	-	-	**-2.3***	-	-	-
Tauber et al. [20] 2023	Baseline	66.5 ± 19.1	53.9 ± 17.6	3.2 ± 0.8	NR	12 ± 8.3	6.7 ± 1.8	7.4 ± 3.1	-	-
	Last visit	39.1 ± 16.4	NR	NR	NR	NR	4.7 ± 2.2	NR	9.6	NR
	Difference $_{LV-B}$	**-27.4***	-	-	-	-	**-2***	-	-	-
Tian et al. [14] 2023	Baseline	64.7 ± 15.1	55.8 ± 16.6	2.9 ± 0.8	NR	12.9 ± 7	6.2 ± 1.9	8.4 ± 3.7	-	-
	Last visit	26.1 ± 21.9	25.9 ± 17.8	4.3 ± 2.1	NR	11.9 ± 7.2	2.4 ± 2.7	6.3 ± 3.2	14.1	8.4 ± 1.6
	Difference $_{LV-B}$	**-38.6***	**-29.9***	**1.4***	-	**-1***	**-3.8***	**-2.1***	-	-
	Mean ± SD	**-24 ± 10.3[a]**	**-14.9 ± 10.9 [a]**	**3.6 ± 1.6 [a]**	**16.7 ± 4.2 [a]**	-	**-2.1 ± 0.9 [a]**	-	**12.9 ± 2.4 [b]**	-

B, Baseline; EDS, Eye dryness score based on a visual analog scale; LLT, Lipid layer thickness; LV, Last visit; NR, Not reported; OSDI, Ocular surface disease; SD, Standard deviation; ST, Schirmer test; TBUT, tear break-up time; tCFS, Total corneal fluorescein staining; TEAEs, Treatment-emergent adverse events.

* Statistical significance level $P < 0.05$.

[a] Mean ± SD values of the difference $_{LV-B}$ for each variable.

[b] Mean ± SD $_{LV}$ value for ocular TEAEs

Table 3
Baseline, Last visit and Differences (Last visit - Baseline) outcomes in the control group.

Author (Date)	Assessment	EDS (0-100)	OSDI (0-100)	TBUT, s	LLT, μm	ST, mm	tCFS (0-15)	Meiboscore (0-15)	Ocular TEAEs, %	Satisfaction (0-10)
Schmidl et al. [12] 2020	Baseline	32 ± 14	40 ± 14	9.4 ± 5.4	71.4 ± 16.3	NR	3.8 ± 1,4	NR	-	-
	Last visit	20.2 ± 17.3	30.4 ± 21.6	14.8 ± 5.3	83 ± 16.4	NR	3.1 ± 1.6	NR	20.8	NR
	Difference $_{LV-B}$	**-11.8**	**-9.6**	**5.7***	**11.6**	-	**-0.7**	-	-	-
Tauber et al. [18] 2021	Baseline	66.8 ± 21.7	54 ± 16.9	3 ± 0.9	NR	14.3 ± 8.8	6.7 ± 2	8 ± 3.9	-	-
	Last visit	56.8 ± 18.7	51 ± 9.2	NR	NR	NR	5.8 ± 1.8	NR	11.7	NR
	Difference $_{LV-B}$	**- 10.7***	**-3**	-	-	-	**-0.9***	-	-	-
Habbe et al. [19] 2023	Baseline	NR	NR	9.9 ± 5.3	51.3 ± 6.7	NR	NR	NR	-	-
	Last visit	NR	NR	15.5 ± 5.6	50.4 ± 5.5	NR	NR	NR	NR	NR
	Difference $_{LV-B}$	-	-	**5.6***	**-0.9**	-	-	-	-	-
Sheppard et al. [13] 2023	Baseline	64.3 ± 19.5	55.8 ± 17.2	3.1 ± 0.9	NR	12.8 ± 7.9	7.1 ± 2.1	8.1 ± 3.5	-	-
	Last visit	45.3 ± 16.5	NR	NR	NR	NR	6 ± 1.9	NR	12.3	NR
	Difference $_{LV-B}$	**-19***	-	-	-	-	**-1.1***	-	-	-
Tauber et al. [20] 2023	Baseline	66.8 ± 18.7	54.4 ± 17	3.3 ± 0.8	NR	11 ± 7.6	6.7 ± 1.9	7.7 ± 3.2	-	-
	Last visit	47.1 ± 17.4	NR	NR	NR	NR	5.7 ± 2	NR	7.5	NR
	Difference $_{LV-B}$	**-19.7***	-	-	-	-	**-1***	-	-	-
Tian et al. [14] 2023	Baseline	65.6 ± 16.5	56.2 ± 16.6	2.8 ± 0.9	NR	13.2 ± 7	6.3 ± 1.7	8.4 ± 3.8	-	-
	Last visit	37.3 ± 20.9	32.3 ± 17.3	4.1 ± 2.3	NR	13.5 ± 6.2	3.6 ± 2.4	6.6 ± 3.5	15.4	7.5 ± 2.0
	Difference $_{LV-B}$	**-28.3***	**-23.9***	**1.3***	-	**0.3**	**-2.7***	**-1.8***	-	-
	Mean ± SD $_{LV-B}$	**-17.9 ± 6.4[a]**	**-12.2 ± 8.7[a]**	**4.2 ± 2.1[a]**	**5.4 ± 6.3[a]**	-	**-1.3 ± 0.7[a]**	-	**13.5 ± 4.4[b]**	-

B, Baseline; EDS, Eye dryness score based on a visual analog scale; LLT, Lipid layer thickness; LV, Last visit; NR, Not reported; OSDI, Ocular surface disease; SD, Standard deviation; ST, Schirmer test; TBUT, tear break-up time; tCFS, Total corneal fluorescein staining; TEAEs, Treatment-emergent adverse events.

* Statistical significance level $P < 0.05$.

[a] Mean ± SD values of the difference $_{LV-B}$ for each variable.

[b] Mean ± SD $_{LV}$ value for ocular TEAEs

Table 4
Inter-group differences [T group $_{LV-B}$) – (C group $_{LV-B}$)] outcomes.

Author (Date)	Assessment	EDS (0-100)	OSDI (0-100)	TBUT, s	LLT, μm	ST, mm	tCFS (0-15)	Meiboscore (0-15)	Ocular TEAEs, %	Satisfaction (0-10)	F/A
Schmidl et al. [12] 2020	T difference $_{LV-B}$	-12.8	-10.6	5.1*	12.5	-	-1.3	-	17.6	-	
	C difference $_{LV-B}$	-11.8	-9.6	5.7*	11.6	-	-0.7	-	20.8	-	F
	Difference $_{T-C}$	**-1**	**-1**	**-0.6**	**0.9**	-	**-0.6**	-	**-3.2[a]**	-	
Tauber et al. [18] 2021	T difference $_{LV-B}$	-11.8*	-4.3	-	-	-	-1.2*	-	11.4	-	
	C difference $_{LV-B}$	-10.7*	-3	-	-	-	-0.9*	-	11.7	-	F
	Difference $_{T-C}$	**-1.1**	**-1.3**	-	-	-	**-0.3**	-	**-0.3[a]**	-	
Habbe et al. [19] 2023	T difference $_{LV-B}$	-	-	4.5*	20.9*	-	-	-	NR	-	
	C difference $_{LV-B}$	-	-	5.6*	-0.9	-	-	-	NR	-	F
	Difference $_{T-C}$	-	-	**-1.1**	**21.8**	-	-	-	-	-	
Sheppard et al. [13] 2023	T difference $_{LV-B}$	-29.5*	-	-	-	-	-2.3*	-	12.9	-	
	C difference $_{LV-B}$	-19*	-	-	-	-	-1.1*	-	12.3	-	F
	Difference $_{T-C}$	**-10.5**	-	-	-	-	**-1.2**	-	**-0.6[a]**	-	
Tauber et al. [20] 2023	Baseline	-27.4*	-	-	-	-	-2*	-	9.6	-	
	Last visit	-19.7*	-	-	-	-	-1*	-	7.5	-	F
	Difference $_{T-C}$	**-7.7**	-	-	-	-	**-1**	-	**2.1[a]**	-	
Tian et al. [14] 2023	T difference $_{LV-B}$	-38.6*	-29.9*	1.4*	-	-1*	-3.8*	-2.1*	14.1	8.4	
	C difference $_{LV-B}$	-28.3*	-23.9*	1.3*	-	0.3	-2.7*	-1.8*	15.4	7.5	F
	Difference $_{T-C}$	**-10.3**	**-6**	**0.1**	-	**-1.3**	**-1.1**	**-0.3**	**-1.3[a]**	**0.9[a]**	

B, Baseline; EDS, Eye dryness score based on a visual analog scale; F/A, Favor or against; LLT, Lipid layer thickness; LV, Last visit; NR, Not reported; OSDI, Ocular surface disease; SD, Standard deviation; ST, Schirmer test; TBUT, tear break-up time; tCFS, Total corneal fluorescein staining; TEAEs, Treatment-emergent adverse events.

* Statistical significance level $P < 0.05$.

[a] Inter-group differences [(T group $_{LV}$) – (C group $_{LV}$)] outcomes.