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REVIEW

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Perfluorohexyloctane ophthalmic solution for the treatment of dry eye disease: a narrative review

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ABSTRACT

Introduction: Dry eye disease (DED) is a common ocular disorder that adversely affects patients' quality of life and daily functioning. Perfluorohexyloctane (PFHO) ophthalmic solution is the first prescription eye drop in the United States that directly targets tear film evaporation. This review synthesizes current evidence on the physiochemical properties, anti-evaporative action and clinical evidence for PFHO.

Areas covered: This review describes the chemical properties of PFHO and explores how these properties relate to the mechanism of action, efficacy, and tolerability of PFHO in DED. PFHO has been shown in clinical trials to be well tolerated and to provide rapid symptom relief, as well as sustained improvement in signs and symptoms of evaporative DED.

Expert opinion: PFHO ophthalmic solution is water-free, preservative-free, pH-free, thermally and chemically stable, and biologically inert; does not scatter or absorb visible light (thus, it has a low likelihood of causing visual disturbance on instillation); has high oxygen-carrying capacity; is slow to evaporate; is a liquid that spreads well over an aqueous surface and forms a barrier at the air-tear film interface that inhibits evaporation of the tear film. These properties contribute to the favorable tolerability, safety, and efficacy of PFHO in patients with DED.

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KEYWORDS
Dry eye disease; evaporative dry eye; meibomian gland dysfunction; semifluorinated alkane; tear evaporation

1. Introduction

Dry eye disease (DED) is a multifactorial disorder characterized by a disruption of the tear film and/or ocular surface homeostasis and accompanied by symptoms that may include ocular discomfort and visual disturbance [1]. Excessive tear evaporation, most commonly due to Meibomian gland dysfunction (MGD), is a causative factor for more than 85% of cases of DED [1,2]. Inadequate tear production, ocular surface inflammation and damage, and neurosensory abnormalities may also contribute. The symptoms of DED adversely affect patients' quality of life and impair daily activities, such as reading and driving [3–5]. DED affects an estimated 8.1% of the US population [6] and 11.6% of people worldwide [7]. In the United States, DED ranks among the most common reasons why patients seek eye care [8].

In patients with DED, treatment aims to restore homeostasis of the ocular surface microenvironment, thereby improving signs and symptoms [2,9]. Management of DED typically follows a stepwise approach, starting with patient education, identification and potential modification of contributing medications and environmental factors, eyelid hygiene, warm compresses, and use of over-the-counter ocular lubricants (eg, artificial tears) [9]. When these initial steps are insufficient, recommended management progresses to prescription medications and office-based therapies. The recent Dry Eye Workshops (DEWS) III report highlights the need for identification of DED etiologic drivers such as tear film deficiencies, ocular surface abnormalities, eyelid anomalies, and systemic drivers, with proposed clinical tests and cutoff values to identify each patient's etiological drivers and inform appropriate management and therapy [1].

2. Overview of the market

Medications approved by the US Food and Drug Administration (FDA) to treat DED include cyclosporine (0.05% ophthalmic emulsion [10], 0.09% ophthalmic solution [11], and 0.1% ophthalmic solution [12]), lifitegrast 5% ophthalmic solution [13], perfluorohexyloctane (PFHO) ophthalmic solution [14], acoltremon ophthalmic solution 0.003% [15], and varenicline solution nasal spray [16]. Additionally, the corticosteroid loteprednol etabonate ophthalmic suspension 0.25% is indicated for short-term (up to 2 weeks) treatment of signs and symptoms of DED [17]. While the precise mechanism of action varies, these medications, with the exception of PFHO, generally work by increasing tear production (cyclosporine, acoltremon, and varenicline) and/or reducing inflammation (cyclosporine, lifitegrast, and loteprednol) [2,10–13,15–18]. PFHO ophthalmic solution is the first prescription eye drop that directly targets tear evaporation [19–21].

Surveys of patients and eyecare professionals have identified the following as key unmet needs in the management

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Article highlights

- Perfluorohexyloctane (PFHO) ophthalmic solution is the first FDA-approved prescription eye drop for dry eye disease (DED) that targets tear evaporation.
- PFHO rapidly spreads across the ocular surface following instillation and forms a barrier at the air – tear film interface that inhibits evaporation of the tear film.
- PFHO has been shown in clinical trials to provide rapid symptom relief, as well as sustained improvement in signs and symptoms of DED.
- PFHO was well tolerated in clinical trials, probably attributable to its lack of pH, the absence of preservatives, and a refractive index similar to that of tears/water.
- The unique physicochemical properties of PFHO position it as a beneficial first-line treatment option for patients with DED.

of DED: rapid relief of DED symptoms, educating clinicians about the importance of addressing all components of DED, enhancing provider understanding of evaporative DED, and development of therapies that target underlying causal factors beyond inflammation [22–24]. During an expert panel assembled in 2020 to discuss advances in knowledge and unmet needs in DED [23], clinicians reported that a common challenge to continued use with some of the available prescription drugs was the slow onset of action, requiring weeks or months before patients perceived a benefit. PFHO has the potential to address unmet needs based on its unique mechanism of action that directly targets tear evaporation [21] and its ability to provide rapid relief of DED symptoms [25]. The aim of this review is to provide a comprehensive analysis of how the chemistry and pharmacology of PFHO translate into reduced signs and symptoms of evaporative DED and a favorable safety profile.

3. Methods

This article followed the SANRA guidelines for narrative review publications [26]. PubMed was searched through 30 June 2025, using the following search string: ('perfluorohexyloctane' OR 'F6H8'). Searches were limited to English-language articles. Reference lists of selected articles also were reviewed to identify additional relevant publications. Articles (including preclinical research, randomized and observational clinical trials, meta-analyses and review articles) relevant to the physicochemical properties of the PFHO molecule, its pharmacokinetics and pharmacodynamics, and the efficacy, safety and tolerability of PFHO ophthalmic solution in the treatment of patients with DED were selected for inclusion in this narrative review. Evidence was synthesized qualitatively, emphasizing mechanistic insights and clinical findings across study types. As a narrative review, no formal risk of bias assessment or quantitative pooling was performed. As this article is based on previously conducted studies, ethical approval was not needed.

4. Chemistry

4.1. Structure

PFHO (also called F6H8; molecular formula, $C_{14}H_{17}F_{13}$) belongs to the class of semifluorinated alkanes (SFAs) that contain a fluorocarbon segment and a hydrocarbon segment connected by a covalent bond (Figure 1) [14,27]. No phase transitions between −10°C and 80°C were observed in an infrared spectroscopic study of PFHO [28]. The high CH_2 stretching frequency of PFHO indicates that at physiological temperature, PFHO is a liquid and not a gel or liquid crystal [29], unlike some other semifluorinated hydrocarbons [30–36]. These findings are in agreement with an earlier study, which showed that the molecular volume (ie, the space occupied by one mole of a substance) of PFHO increased linearly with temperature, with no sharp increase or decrease that would be expected with a phase change [37]. PFHO has been shown in vitro to spread well over an aqueous surface and a 125-nm-thick film of meibum [29]. This is consistent with its low surface tension (between 5 mN/m [38] and 14 mN/m [39]), which allows it to spread well at a rate of 0.89 cm^2/s [29]. These properties contribute to the ability of PFHO to form a protective, evaporative-resistant, hydrophobic, thin layer on the ocular surface (discussed later in this article).

4.2. Physical properties

PFHO ophthalmic solution is a single-component, nonaqueous eye drop [40]. The physicochemical properties of PFHO and other SFAs, such as density, boiling point, viscosity, vapor pressure, and surface tension, have been reviewed previously [41]. Insights from early structure-function investigations of SFAs and recent studies evaluating the anti-evaporative properties of PFHO provide the mechanistic foundation for how PFHO forms a stable, biocompatible, evaporation resistant monolayer on the ocular surface. As is the case with SFAs in general, PFHO is thermally and chemically stable and physiologically inert [42–44], which are advantageous properties for an ophthalmic eye drop. Because it does not contain water, PFHO does not have an aqueous pH value. PFHO also does not require a preservative since it cannot support microbial growth. The lack of a pH value and preservatives, both of which may cause ocular irritation, represent an advantage over aqueous eye drops, especially those that contain preservatives [40,45,46]. The chemical and physiological inertness of PFHO may also reduce the risk of ocular irritation [40].

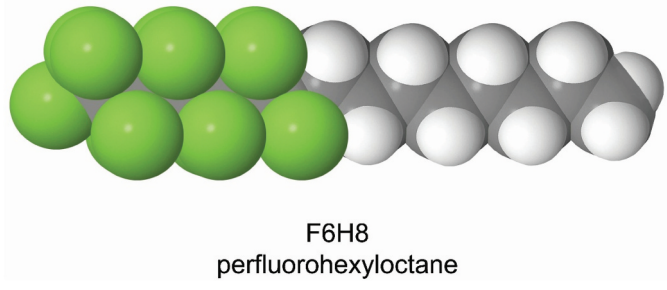


Figure 1. Space filling models of perfluorohexyloctane. White balls are hydrogen atoms, gray balls are carbon atoms, and the green balls are fluorine atoms. The nomenclature for semifluorinated alkanes is FnHm, where n is the number of fluorinated carbons, and m is the number of protonated carbons.

In a spectroscopy study, PFHO was not observed to scatter or absorb visible light in contrast to emulsion eye drops which had a very high optical density and low light transmission (Figure 2) [28]. The refractive index of PFHO is similar to that of tear fluid (1.336–1.338) and, thus, would be expected to cause minimal visual blurring when applied to the eye [47–49], in contrast to many oil-containing eye drops that have higher refractive indices [48,49].

Recently, it has been suggested that the tear film lipid layer (TFLL) plays a role in corneal oxygenation [50]. As expected of an SFA, PFHO has the capacity to contain a significant amount of oxygen as demonstrated using fluorine-19 nuclear magnetic resonance spectra to measure the interaction of oxygen molecules with the fluorine molecules of PFHO. The mean partial pressure of oxygen was calculated as 270 mm Hg at 37°C which is higher than the surface of the corneal epithelium (155 mm Hg). This data suggests that, like the TFLL, once instilled onto the ocular surface, PFHO is not a barrier to the oxygen necessary for a healthy cornea. Conversely, PFHO may serve as a source of nonreactive oxygen to facilitate healing in patients with DED [51].

PFHO is amphiphilic (the perfluorocarbon and hydrocarbon segments have different affinities), amphisteric (the 2 segments have different conformations and space requirements), and amphidynamic (the 2 segments have different rigidities) [52]. The perfluorocarbon segment is extremely hydrophobic and lipophobic, while the hydrocarbon segment is less hydrophobic and is also lipophilic. Following instillation, the amphiphilic properties of PFHO allow it to form a long-lasting monolayer at the air – tear film interface that inhibits evaporation of the aqueous portion of the tear film (Figure 3) [19–21]. The bulkier size and rigidity of the perfluorocarbon segment, as compared to the flexibility and smaller hydrocarbon segment, contributes to the ability to self-assemble to form a monolayer at the air – tear interface [19,21,53].

The covalent connection between the two segments of PFHO creates a significant intramolecular dipole moment at the junction. This also contributes to the self-assembling

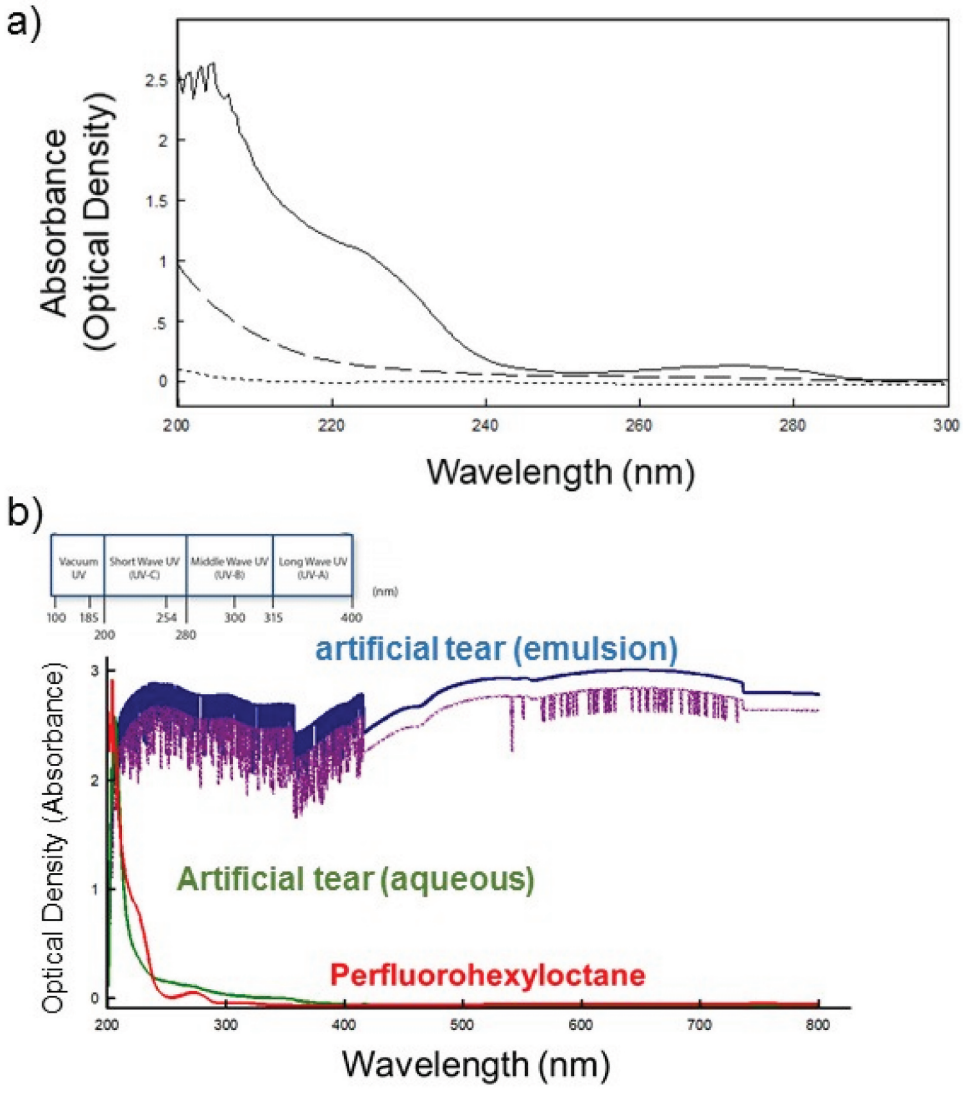
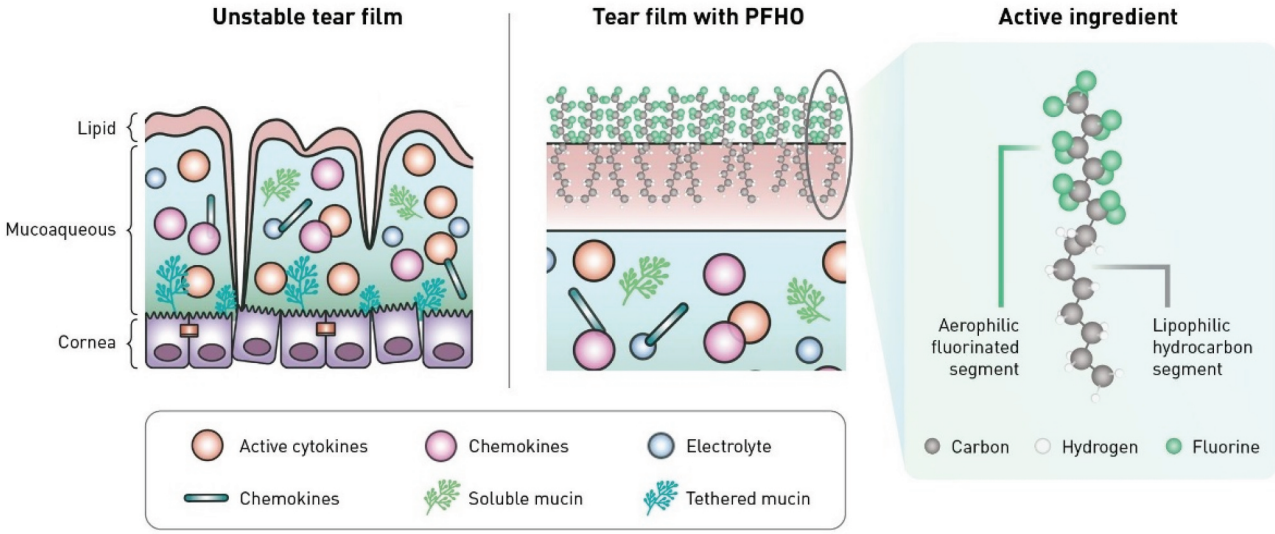


Figure 2. (a) Absorbance spectra of (solid line) perfluorohexyloctane, (dashed line) n-hexane, and (dotted line) perfluorooctane. None of the compounds absorbed light above 300 nm [28]. (b) Absorbance spectra of over-the-counter artificial tears (1 aqueous-based and 2 lipid-based emulsions). A 1-cm path length cuvette was used. The spectra of emulsion artificial tears both had an absorbance greater than 3 (O.D.) between 200 and 800 nm, indicating that less than 1/1000th of the light was transmitted.



PFHO, perfluorohexyloctane.
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Figure 3. PFHO forms a monolayer at the tear film air – liquid interface.
PFHO, perfluorohexyloctane. Figure reproduced with permission from Bausch + Lomb.

properties of PFHO and confers low volatility to the molecule, which is important for its long ocular residence time [54]. PFHO is slow to evaporate (0.00015 g/min at 35 °C) [27,54], 40 times slower than the shorter-chain SFA perfluorobutylpentane (F4H5) that has been used as a vehicle to facilitate delivery of cyclosporine to the ocular surface [55,56]. At a physiological temperature, less than 50% of PFHO evaporated, even after 24 hours [54]. The slow evaporation rate of PFHO relative to shorter-chain SFAs is due, in part, to the molecular dipole moment with respect to the main axis [57] and an unequal electron distribution, which occurs as electrons temporarily shift within the PFHO molecule, generating a small, negative charge on one side of the segments and a small, positive charge on the opposite side [27]. The transient negative and positive charges result in hydrophobic van der Waals interactions between fluorocarbon and hydrocarbon segments. Stronger molecular forces (eg, van der Waals interactions) result in lower volatility and vapor pressure, thus reducing evaporation rate. Accordingly, in a recent study of SFAs with varying chain lengths, hydrocarbon and fluorocarbon chain lengths were found to be related to the SFA's inherent dipole moment, boiling point, and evaporation rate [27].

PFHO spreads rapidly across the ocular surface after instillation due to its very low surface tension. Ex vivo evaluation of the interaction of PFHO with the corneal surface using high-speed photography demonstrated that complete deposition occurred within 20 msec of drop contact with the cornea [20]. When accounting for volume differences, PFHO spread across an area approximately 2.5 times greater than that for saline.

PFHO emits infrared light very intensely, which allows dynamic visualization of its spread and residence time on the ocular surface using high-resolution infrared detection technology. Visualization of PFHO spreading using infrared emissivity demonstrated that PFHO spread rapidly over the top of meibum to form a layer that lasted for >3 hours in a static in vitro model. Following a single instillation in a volunteer without DED, PFHO remained on the ocular surface for >5 hours, demonstrating its ability to form a long-lasting, anti-evaporative layer on the surface of the tear film [29]. Similar results were observed among 10 participants without DED and 4 with DED (Figure 4) [58]. The longer residency time of PFHO in vivo versus in vitro is not unreasonable, in that the turnover of the TFLL is 10 times slower (0.93%/min) compared with the aqueous portion of tears (10.3%/min) [59].

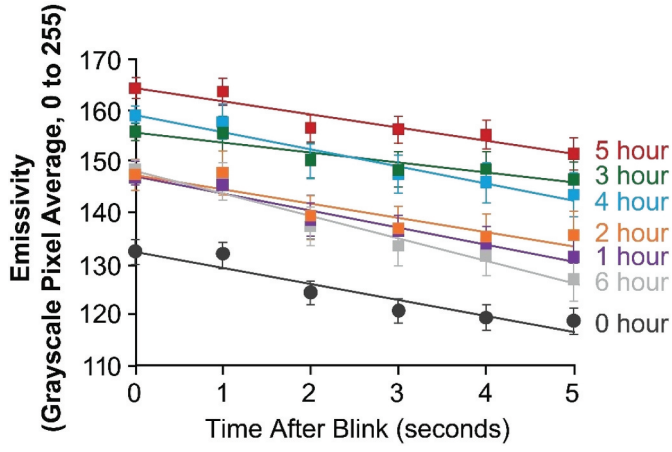

Figure 4. Elevated emissivity intensity *in vivo*, measured 1, 2, 3, 4, and 5 seconds after blinking, at timepoints 1 to 6 hours after administration of PFHO [58]. Ten subjects without DED were examined. Error bars are the standard error of the mean; $p < 0.001$ vs preinstillation at all timepoints. DED, dry eye disease; PFHO, perfluorohexyloctane.

5. Pharmacodynamics

A standard gravimetric assay with a surface area similar to that of the human eye was used to demonstrate the ability of PFHO to inhibit evaporation of phosphate-buffered saline (PBS) [21]. At 35°C, PFHO inhibited the rate of evaporation of PBS by 28% after applying a single 11-µL drop (the clinical dose/drop size of PFHO), and by 88% when layering 100 µL of PFHO on top of PBS (both $p < 0.0001$) – approximately 4 and 10 times, respectively, greater than human meibum (8%; Figure 5(A)). PFHO is unique among eye drops, in that 100 µL of PFHO layered over PBS inhibited the evaporation rate of PBS by 82% at 25°C ($p < 0.0001$), whereas artificial tears did not significantly affect PBS evaporation (Figure 5(B)). In another study, adding an equivalent of 1.7 µL to the ocular surface inhibited evaporation by approximately 10% [38]. A study evaluating SFAs with hydrocarbon segments ranging from 2 to 10 carbons and perfluorinated chain lengths of 4 or 6 carbons demonstrated that the anti-evaporative effect was dependent on chain length [27]. When layering 100 µL of the SFAs, longer-chain SFAs F6H8 (PFHO) and F6H10 inhibited evaporation, while shorter-chain SFAs (F4H2, F4H5, and F6H7) had minimal or no effect (Figure 5(C)). Furthermore, when 11 µL of SFAs was layered on the surface of saline, only PFHO inhibited R_{evap} of PBS.

Clinical trials have assessed the ability of PFHO to stabilize the tear film in patients with DED. In 48 patients with mild-to-moderate DED, PFHO (n = 24) instilled in both eyes 4 times daily (QID) over 4 weeks significantly increased tear film and TFLL thickness relative to saline (n = 24) [60]. A randomized trial that included 37 patients with DED randomized to PFHO (n = 18) or a cationic nanoemulsion of mineral oil (CN, n = 19), each instilled 5 times per day over 12 weeks, and 15 untreated controls without DED, found that lipid layer thickness increased significantly during treatment with PFHO. However, differences between the PFHO

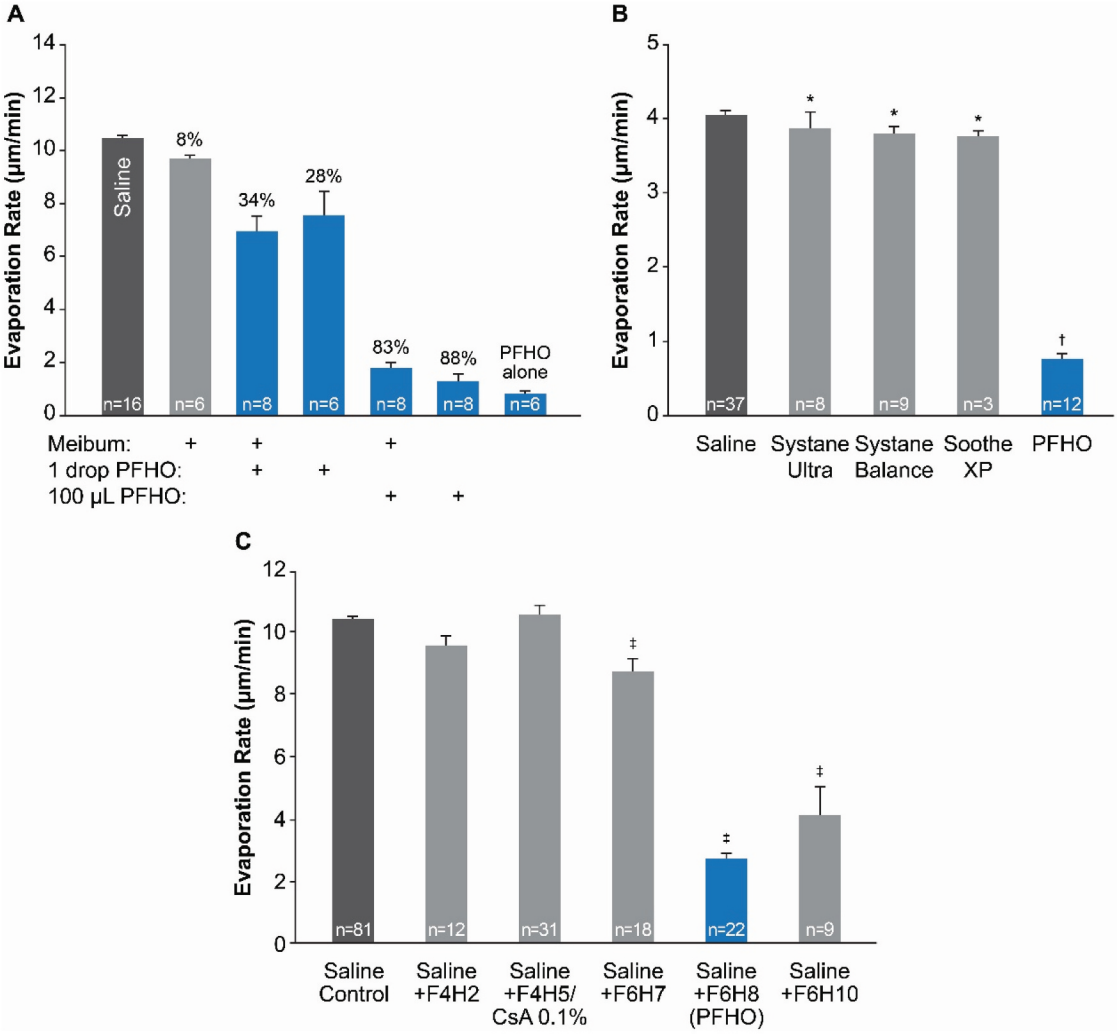

Figure 5. In vitro evaporation rates of phosphate-buffered saline (PBS) under various conditions [21,27]. (A) Evaporation rates of PBS alone, perfluorohexyloctane (PFHO) alone, and PBS overlayed with human meibum, with and without the addition of an 11-µL drop or 100 µL of PFHO layered on top at 35°C. Meibum was obtained from a 68-year-old Caucasian male. Percentage values are the % inhibition of the R_{evap} of PBS. $p < 0.0001$ vs saline control for all (B) Evaporation rates of PBS alone and with 100 µL of various over-the-counter eye drop samples and PFHO placed on top at 25°C. (C) Evaporation rates of PBS with and without the addition of 100 µL of semifluorinated alkanes with differing chain lengths, layered on the surface at 35°C [27]. The F4H5 sample contained 0.1% cyclosporine. *Not significant ($p > 0.05$ vs saline), $^{\dagger}p < 0.001$ vs saline, $^{\ddagger}p < 0.0001$ vs saline. N values represent the number of determinations. *P*-values to test for significance were measured using Student's *t* test. Error bars are the standard error of the mean. Figures 5(A,B) adapted with permission from Vittitow J, et al. Curr Ther Res Clin Exp. 2023;98:100704.

group and the other treatment groups at 12 weeks were not statistically significant [61]. Similarly, in a randomized trial comparing PFHO QID [n = 10] with 2 water-based lubricant eye drops administered QID [n = 10 each], PFHO was associated with a significant increase from baseline in lipid layer thickness, but differences between treatment groups were not statistically significant [62]. Taken together, these in vitro and in vivo data demonstrate the ability of PFHO to mimic the anti-evaporative function of the TFLL, resulting in improved stability of the tear film in patients with evaporative dry eye.

In addition to stabilizing the tear film, PFHO appears to reduce the corneal surface temperature (CST), resulting in increased blinking and tearing as a reflex driven by TRPM8-mediated activation of cold-sensitive receptors in the cornea [63]. Bilateral topical instillation of PFHO into the eyes of 7 healthy volunteers significantly decreased CST at 5, 15, and 60 minutes (but not 30 minutes) post-instillation, without evoking any conscious ocular sensations, whereas bilateral instillation of saline did not affect CST. Blinking frequency significantly increased following bilateral instillation of PFHO. In 6 separate participants, a transient increase in tearing, as assessed with phenol red threads, was observed at 5 minutes after PFHO instillation, although the change was not statistically significant. The increased blinking frequency may contribute to the benefits of PFHO in DED by resulting in more frequent redistribution of tears over the ocular surface.

6. Pharmacokinetics and metabolism

Following topical ocular administration of single or multiple doses of radiolabeled PFHO in rabbits, exposure (maximum concentration, area under the concentration-time curve) of PFHO was highest in tears (single dose: 2300 µg/g, 3050 µg • h/g; multiple doses: 2330 µg/g, 3720 µg • h/g) and Meibomian glands (single dose: 294 µg/g, 674 µg • h/g; multiple doses: 222 µg/g, 1440 µg • h/g; Figure 6) [64]. The concentration of PFHO in tears and Meibomian glands peaked at 15 minutes after single-dose administration and remained detectable for up to 8 hours in tears and for at least 24 hours in Meibomian glands. Substantial concentrations of PFHO were also observed in other anterior tissues, including the lacrimal glands, cornea, conjunctiva, and sclera. In posterior segment tissues, distribution was minimal, and maximum concentrations were similar after single- or multiple-dose administration, indicating little drug accumulation with repeat dosing. Quantitative whole-head autoradiography confirmed results of the pharmacokinetic (PK) analysis and additionally detected PFHO in the nasal turbinates and nasolacrimal duct. Systemic exposure was negligible, based on levels of radiolabeled PFHO in blood and plasma, as well as on whole-body autoradiography. Consistent with this finding, a phase 2 trial in patients with DED found that more than 70% of blood samples had no measurable PFHO following ocular administration, and remaining samples had concentrations just above the limit of quantification (1 ng/mL) [65].

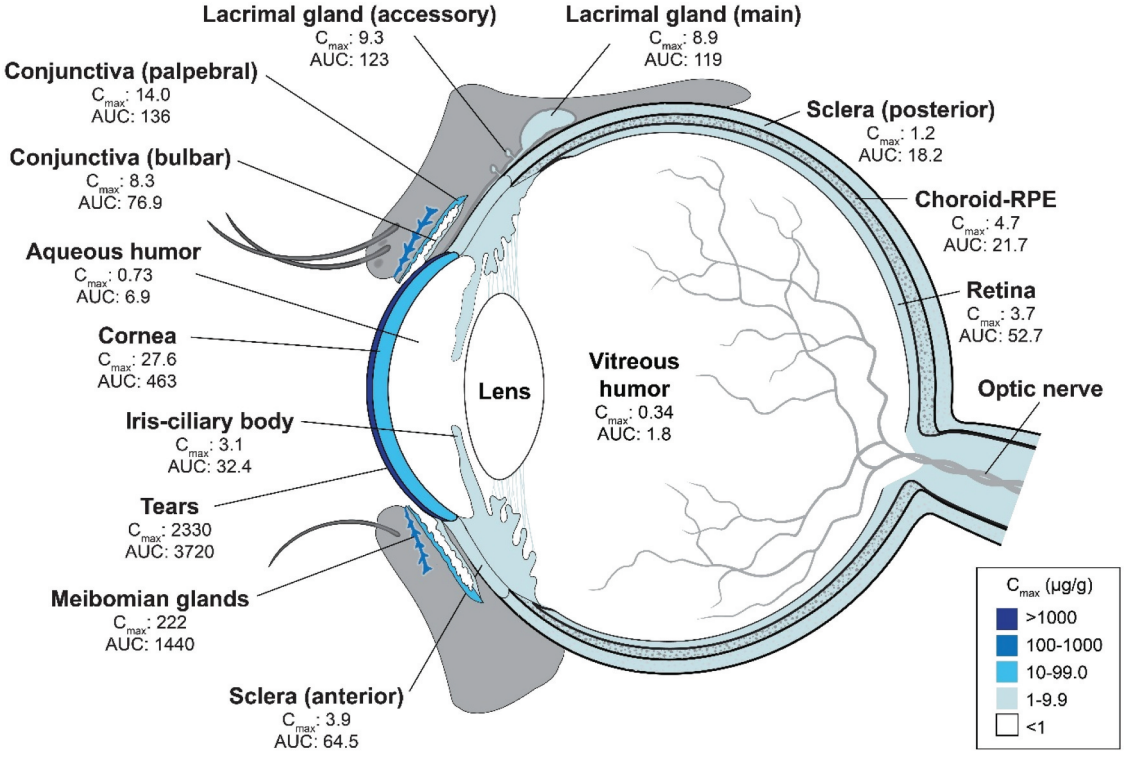

Figure 6. Ocular distribution of PFHO after repeated topical administration [64]. Samples were taken from 2 animals (4 eyes) at each timepoint on day 5 (0.25, 0.5, 1, 2, 4, 8, and 24 h). Data represent mean values. AUC, area under the concentration time curve from time 0 to the last measurable timepoint, measured in µg • h/g; C_{max}, maximum concentration, measured in µg/g; PFHO, perfluorohexyloctane; RPE, retinal pigment epithelium. Figure 6 reprinted from Krösser S, et al. J Ocular Pharmacol Ther. 2025;41(7):370–377. Under the terms of the Creative Commons License [CC-BY] https://creativecommons.org/licenses/by/4.0/.

Single or repeated oral dosing of PFHO in rodents resulted in little absorption, with up to 70% of the administered dose excreted in feces and only minimal levels recovered in urine and bile, suggesting that renal and biliary excretion are not routes of elimination [66]. In vitro studies indicate that PFHO is unlikely to be metabolized by human liver microsomes [14]. Based on these studies, and consistent with its immiscibility with water and nonreactive nature, PFHO instilled on the eye does not bioaccumulate in tissues. Following administration, it is cleared from the body unchanged, either by evaporating slowly from the ocular surface into the air or by entering the gastrointestinal tract via lacrimal drainage and being excreted in feces. Any small amounts of PFHO that are absorbed systemically following topical instillation are excreted via exhalation [65,67].

In a preclinical study in rabbits, prior administration of a single topical ocular dose of PFHO did not affect the ocular PK profile of latanoprost acid or prednisolone, suggesting that PFHO would not impact the efficacy of these medications [68]. These findings indicate that the presence of PFHO on the ocular surface would not likely affect absorption of other topical eye drops in patients with DED taking multiple medications.

7. Efficacy of PFHO for the treatment of DED

Four multicenter, randomized, saline-controlled, phase 2 and 3 clinical trials evaluated the efficacy of PFHO (Miebo; Bausch + Lomb, Bridgewater, NJ, U.S.A.; Heng Qin; Hengri Pharmaceuticals, Shanghai, China) in patients with DED associated with MGD (Table 1) [65,69–71]. In all studies, PFHO was instilled 4 times daily (QID); the phase 2 study also evaluated twice daily dosing (BID) and the comparator was either 0.6% or 0.9% saline at the same dosing regimen(s). All four studies were multicenter, double-masked, with an 8-week follow-up and identical key inclusion criteria (tear film break up time ≤ 5 s; Schirmer score ≥ 5 mm; Ocular Surface Disease Index ≥ 25; total corneal fluorescein staining [tCFS] ≥4-≤11 (on a 0–15 NEI scale); MGD score ≥ 3 (on a 0–15 scale).

In the phase 2 study (SEECASE; n = 336), PFHO instilled BID or QID demonstrated significantly greater reduction in the signs (tCFS) and symptoms (eye dryness score [EDS]) of DED compared with isotonic saline (0.9% solution) as early as week 2 of treatment, with continued improvement observed through week 8 [65]. Consistent with the results from SEECASE, the pivotal, similarly designed, phase 3 studies (GOBI [n = 597] and MOJAVE [n = 620]) in US patients with DED met both sign and symptom primary efficacy endpoints with significantly greater reductions in the PFHO group (instilled QID) compared with the hypotonic saline (0.6% solution) control group in tCFS and EDS at week 8 [69,70]. Furthermore, significant differences between treatment groups in tCFS and EDS were observed as early as week 2. Significant improvements in tCFS and EDS with PFHO versus hypotonic saline (0.6% solution) were also demonstrated at week 8 in another similarly designed but independent phase 3 study in Chinese adults with DED (n = 312) [71]. For the primary endpoints of EDS and tCFS the improvements in the PFHO arm over the saline control ranged from 8–13 and 1.0–1.2 points, respectively, across the four studies (Table 1). This magnitude of difference over the control is generally considered to be a clinically meaningful improvement in the treatment of DED.

A meta-analysis of the phase 2 and 3 clinical trials also included data from a 4-week, phase 4, single-center, randomized, single-masked (observer-blinded) trial (NCT0304852) [60] in adults with mild-to-moderate DED who received PFHO (NovaTears; AFT Pharmaceuticals, Auckland, New Zealand) or saline 0.9% in both eyes QID [72]. This meta-analysis, involving 1802 patients, highlights the efficacy of PFHO in ameliorating the signs and symptoms of DED. Patients received PFHO (n = 908) or a saline solution for comparison (n = 894), administered QID for 8 weeks in the phase 2/3 trials and for 4 weeks in the phase 4 trial. Compared with saline solution, PFHO significantly ($p < 0.001$) reduced tCFS, with a pooled standardized mean difference (SMD; 95% CI) of −0.53 (0.68, −0.38), and also reduced EDS, with a pooled SMD (95% CI) of −0.49 (−0.66, −0.32) [60] (Supplementary Figure S1). Statistically significant improvements in tCFS and EDS with PFHO versus saline were observed at day 15, the earliest post-baseline assessment (Table 1).

A 52-week, phase 3, multicenter, single-arm, open-label extension study (KALAHARI) evaluated the long-term efficacy of PFHO [73]. KALAHARI enrolled 208 patients who completed the phase 3 GOBI trial without any major protocol violations. Among patients assigned to PFHO in GOBI who continued to use PFHO during KALAHARI (n = 97), improvements in tCFS and EDS scores observed during the 8-week GOBI trial were maintained throughout the open-label extension study (60 weeks total across studies). Patients assigned to saline during GOBI who switched to PFHO in KALAHARI (n = 111) experienced improvements in tCFS and EDS scores by week 4 that were sustained through week 52. Mean ocular symptom scores improved relative to GOBI baseline throughout the extension study.

In the phase 2 and 3 trials of PFHO, changes from baseline in signs and symptoms of DED were not assessed prior to day 15 [25]. A prospective, multicenter, open-label, phase 4, postmarketing trial evaluated patient-reported outcomes over the first 2 weeks of PFHO treatment in 99 adults with DED [25]. Patients instilled PFHO into both eyes QID for 14 days. Patient-reported severity of overall and individual DED symptoms decreased significantly from baseline through day 14, with significant improvement observed as early as 5 minutes after dosing on day 1 (Figure 7). Overall symptom severity decreased by 56.3% at 1 hour after treatment on day 1 and continued to decrease, reaching a 61.7% reduction from baseline at day 7 (primary endpoint) and 65.9% at day 14. Similarly, patient-reported frequency of the most bothersome symptom decreased, with significant reductions from baseline at day 3 (40.0% reduction), day 7 (47.0% reduction), and day 14 (55.5% reduction; all $p < 0.0001$). The open-label design of this study can increase the risk of expectation bias and therefore is a study limitation.

Post-marketing studies have investigated the efficacy of PFHO in patients with DED and lid wiper epitheliopathy (LWE) [74], patients with severe DED due to graft versus host disease (GVHD) [75], and patients with DED undergoing cataract surgery [76]. Lid

Table 1. Randomized controlled phase 2 and 3 trials of PFHO ophthalmic solution in patients with DED.

Study			SEECASE (NCT03333057) [65]	MOJAVE (NCT04567329) [69]	GOBI (NCT04139798) [70]	NCT05515471 [71]
Study design and participants			8-week, phase 2, multicenter, randomized, double-masked trial in adults with DED associated with MGD	8-week, phase 3, multicenter, randomized, double-masked trial in adults with DED associated with MGD		8-week, phase 3, multicenter, randomized, double-masked trial in Chinese adults with DED associated with MGD
Treatment groups			Both eyes: • PFHO BID (n = 111) • PFHO QID (n = 114) • Isotonic saline 0.9% BID/QID (combined control; n = 111)	Both eyes: • PFHO QID (n = 311) • Saline 0.6% QID (n = 309)	Both eyes: • PFHO QID (n = 303) • Saline 0.6% QID (n = 294)	Both eyes: • PFHO QID (n = 156) • Saline 0.6% QID (n = 156)
Key efficacy results at week 2 (day 15)	tCFS	CFB	NR	• PFHO: −1.9 • Saline: −1.3	• PFHO: −1.7 • Saline: −1.1	• PFHO: −2.6 • Saline: −2.3
		LS mean (95% CI) Δ vs saline	• PFHO BID: −0.7* (−1.2 to −0.1), $P = 0.018$ • PFHO QID: −0.9* (−1.4 to −0.3), $P = 0.002$	−0.6 (−1.0 to −0.2), $P = 0.001$	−0.6 (−0.9 to −0.2), $P = 0.001$	−0.3 (−0.8 to 0.2), $P = 0.25$
	EDS	CFB	NR	• PFHO: −18.5 • Saline: −10.5	• PFHO: −18.0 • Saline: −13.4	• PFHO: −16.7 • Saline: −12.9
		LS mean (95% CI) Δ vs saline	• PFHO BID: −7.3* (−13.2 to −1.5), $P = 0.015$ • PFHO QID: −11.8* (−17.6 to −6.0), $P < 0.001$	−7.8 (−11.3 to −4.3), $P < 0.001$	−4.7 (−8.2 to −1.2), $P = 0.009$)	−3.8 (−7.4 to −0,2), $P = 0.04$
	OSDI	CFB	NR	• PFHO: −15.8 • Saline: −11.9	NR	• PFHO: −14.7 • Saline: −12.8
		LS mean (95% CI) Δ vs saline	• PFHO BID: −1.8* (−5.9 to 2.4), $P = 0.410$ • PFHO QID: −4.2* (−8.3 to −0.0), $P = 0.048$	$P \leq 0.002$	NR	−1.9 (−5.5 to 1.7), $P = 0.30$
Key Efficacy results at week 8 (day 57)	tCFS	CFB	• PFHO BID: −1.8 • PFHO QID: −2.1 • Saline: −0.9	• PFHO: −2.3 • Saline: −1.1	• PFHO: −2.0 • Saline: −1.0	• PFHO: −3.8 • Saline: −2.7
		LS mean (95% CI) Δ vs saline	• PFHO BID: −0.9* (−1.5 to −0.2), $P = 0.009$ • PFHO QID: −1.2* (−1.8 to −0.6), $P < 0.001$	−1.2 (−1.7 to −0.8), $P < 0.001$	−1.0 (−1.4 to −0.6), $P < 0.001$	−1.1 (−1.7 to −0.6), $P < 0.001$
	EDS	CFB	• PFHO BID: −30.4 • PFHO QID: −31.6 • Saline: −19.7	• PFHO: −29.5 • Saline: −19.0	• PFHO: −27.4 • Saline: −19.7	• PFHO: −38.6 • Saline: −28.3
		LS mean (95% CI) Δ vs saline	• PFHO BID: −10.7* (−17.6 to −3.8), $P = 0.002$ • PFHO QID: −11.8* (−18.7 to −5.0), $P < 0.001$	−10.2 (−14.4 to −6.1), $P < 0.001$	−7.6 (−11.8 to −3.4), $P < 0.001$	−12.7 (−17.2 to −8.3), $P < 0.001$
	OSDI	CFB	NR	• PFHO: −23.3 • Saline: −15.9	NR	• PFHO: −29.9 • Saline: −23.9
		LS mean (95% CI) Δ vs saline	• PFHO BID: −3.0* (−8.0 to −2.0), $P = 0.235$ • PFHO QID: −4.3 (−9.2 to 0.6), $P = 0.087$*	Mean NR, $P \leq 0.002$	NR	−6.0 (−10.0 to −2.0), $P = 0.003$

* Observed mean.

BID, twice daily; CFB, change from baseline; DED, dry eye disease; EDS, eye dryness score; LS, least-squares; MGD, meibomian gland dysfunction; NR, not reported; OSDI, Ocular Surface Disease Index; PFHO, perfluorohexyloctane; QID, 4 times daily; tCFS, total corneal fluorescein staining.

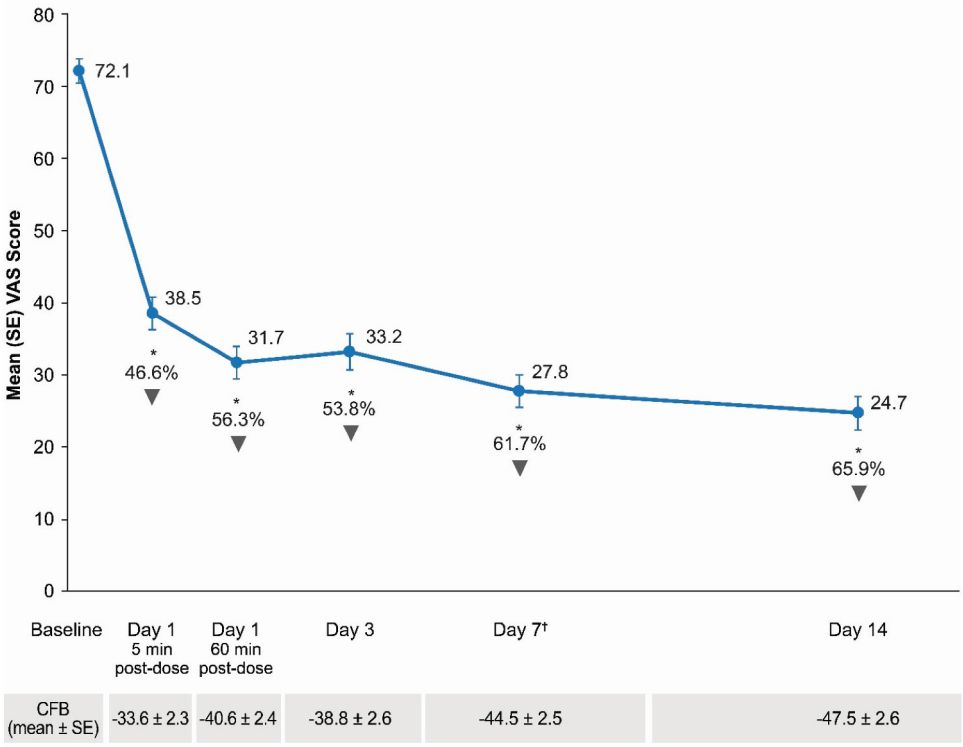

Figure 7. Patient-reported severity of overall dry eye symptoms before and after treatment with PFHO ophthalmic solution 4 times daily [25]. *$p < 0.0001$ versus baseline (paired *t* test). †Primary endpoint. CFB, change from baseline; PFHO, perfluorohexyloctane; SE, standard error; VAS, visual analog scale. Figure adapted with permission from Bacharach J, et al. Ophthalmol Ther. 2025;14:693–704.

wiper epitheliopathy refers to friction-related damage to the marginal epithelium of the upper eyelid (ie, the 'lid wiper'), where it contacts the ocular surface during blinking [77–79]. This condition can result from dysfunctional tear film and is commonly associated with DED. A multicenter, randomized, single (investigator)-masked trial compared PFHO (instilled QID; n = 26) with no treatment (n = 26; control group) in patients with LWE and DED [74]. The authors hypothesized that PFHO may preserve the aqueous layer and reduce friction between the ocular surface and eyelid, consequently improving signs and symptoms related to LWE. The severity of LWE did not differ significantly between treatment groups at baseline but was significantly lower in patients treated with PFHO versus control starting at 2 weeks and for the remainder of the 2-month study (all comparisons, $P < 0.001$). DED symptoms (Standard Patient Evaluation of Eye Dryness [SPEED] scores and EDS scores) were comparable between groups at baseline but were significantly lower in PFHO-treated patients versus untreated controls at 2 weeks (SPEED, $p = 0.005$; EDS, $p < 0.001$), 1 month (SPEED, $p = 0.001$; EDS, $p = 0.003$), and 2 months ($p < 0.001$ for both SPEED and EDS).

In an 11- to 13-week, multicenter, observational study in 25 patients with severe DED due to chronic GVHD, 57% of patients reported fast or very fast relief of symptoms with PFHO [75]. However, treatment with PFHO in the 15 patients who applied medication reliably and completed the study did not result in significant changes in Schirmer test, TFBUT, CFS, meibum secretion (not analyzed statistically), and OSDI (change not clinically significant), possibly, in part, because the participants have tear film lipids that are unusually stiff compared even with participants who have MGD [80–82]. Stiff lipids may block the Meibomian glands from expressing meibum and inhibit their spreading on the tear film surface. In addition, the patients in the pivotal studies had mild to moderate DED and signs of MGD with either mild aqueous deficiency or normal tear production (Schirmer score ≥ 5 mm), while the GVHD patients had severe DED and very low Schirmer scores (~2 mm). The majority of GVHD patients were also already on multiple DED medications including cyclosporine and artificial tears.

A prospective open-label multicenter study evaluated the effects of preoperative treatment with PFHO in 97 patients with DED scheduled for phacoemulsification with posterior chamber intraocular lens (IOL) implantation [76]. Patients instilled PFHO QID for 30 days before surgery and received a second 30-day course of PFHO beginning approximately 1 month postsurgery. The accuracy of predicted refraction, as determined via biometry, was high. Presurgical treatment with PFHO resulted in statistically significant mean (SD) reductions from baseline of −2.9 (2.5) for tCFS and −0.7 (0.9) for central CFS (both $p < 0.0001$). Mean (SD) symptom scores were significantly reduced by −25.2 (21.9) for EDS and −21.4 (16.8) for OSDI (both $p < 0.0001$). Continued improvements in signs and symptoms were observed after the second course of treatment ($p < 0.001$ for all comparisons). These findings demonstrate the predictability of refractive outcomes with PFHO use and the utility of PFHO for reducing signs and symptoms of DED in patients with DED undergoing cataract surgery.

Treatment with PFHO significantly improved contact lens comfort in a 4-week, single-center trial in 47 habitual soft contact lens wearers (≥60 days) without DED symptoms [83]. In accordance with the package insert, participants removed their contact lenses prior to each instillation and waited at least 30 minutes after administration before reinserting their contact lenses. No statistically significant changes in tear film osmolarity, tCFS, or meibography were observed. While these findings suggest that PFHO may increase lens comfort, additional studies are warranted to assess the safety and efficacy of PFHO in contact lens wearers with DED.

8. Safety and tolerability of PFHO

A meta-analysis of data from the four phase 2 and 3 RCTs of PFHO found that 11.7% of patients treated with PFHO QID and 11.1% of those in the saline control groups experienced at least 1 ocular treatment-emergent adverse event (AE), yielding a relative risk (RR [95% CI]) of 1.05 (0.84 to 1.32; $P = 0.506$) [72]. Vision blurring, the most common TEAE, was reported by 2.5% of PFHO-treated patients versus 0.5% of those in the saline control groups (RR [95% CI], 5.10 [2.39 to 10.91]; $P = 0.006$; absolute risk increase: 0.02). Blurred vision was typically mild and transient in the pivotal clinical trials. The percentage of patients who experienced eye pain did not differ significantly between the PFHO (0.9%) and saline control (1.4%) groups (RR [95% CI], 0.68 [0.18 to 2.56]; $P = 0.418$). None of the ocular TEAEs in the phase 2 and 3 RCTs were considered serious, and the rate of discontinuation due to an AE among patients receiving PFHO was very low (0%-1.3% across trials) [65,69–71].

In the phase 3 extension trial (KALAHARI), 29 of 208 patients (13.9%) reported 1 or more ocular AEs over 52 weeks of PFHO treatment. The most common ocular AEs were vitreous detachment (1.9% (4/208], none considered treatment-related by the investigator), allergic conjunctivitis (1.4% [3/208]), blurred vision (1.4% [3/208]), and increased lacrimation (1.4% [3/208]) [73]. Most were mild or moderate in severity. Visual acuity remained stable, and other ocular safety assessments (intraocular pressure, slit-lamp biomicroscopy, and dilated fundoscopy) did not indicate any safety concerns with long-term use of PFHO. Similarly, PFHO was well tolerated in phase 4 studies, with low rates of ocular AEs and no clinically meaningful changes in safety parameters [25,60,74–76,83], including in patients with DED associated with LWE [74] or chronic GVHD [75].

As PFHO does not absorb visible light [28], it is not expected to directly affect vision when instilled onto the ocular surface, consistent with the low rate of blurring experienced in the clinical trials. In addition, PFHO treatment did not affect visual acuity in several clinical studies [60,62,65,69,70,73–75,83,84]. Of 2 clinical trials that assessed higher-order visual aberrations associated with PFHO treatment, one in patients with DED did not detect any significant difference from baseline after 4 or 12 weeks of PFHO treatment [61], whereas the other study showed a small but statistically significant difference after 4 weeks of PFHO treatment (mean [SD] from 0.272 [0.069] at baseline to 0.323 [0.076] at week 4, $p = 0.001$) in healthy eyes [85]. In the latter study, participants did not report any visual disturbances, possibly due to the small increases in higher-order aberrations being clinically imperceptible. In addition, the latter study used different instrumentation from the first study and was in healthy individuals, which may have impacted the results.

Studies indicate high satisfaction with PFHO. In the prospective, phase 4 study described above [25], satisfaction with treatment was high and increased over the 14-day treatment period. In the year-long KALAHARI safety study, patients reported high satisfaction at week 52 and found the study drop to be comfortable and easy to administer [73]. A survey of patients with DED in an electronic health records database who had newly initiated treatment with PFHO (n = 22) or cyclosporine (n = 133) found that 82% of patients who had started PFHO treatment were satisfied with their prescription compared to 59% of those who had initiated cyclosporine treatment [86]. Notably, 82% of PFHO-treated patients renewed their prescription, versus 69% of patients in the cyclosporine group.

9. Other clinical applications of PFHO

Beyond treatment of DED, PFHO has been used clinically as a tamponade for retinal detachment [87,88]. Additionally, potential other clinical applications of PFHO have been reviewed [41], including its use as an oxygen carrier, especially in an organ storage medium [51,89–93], an in vivo oxygen-probe [94], and as a vehicle for drug delivery on the skin and in the lungs [95–98].

10. Regulatory affairs

PFHO ophthalmic solution was approved as a prescription medication for the treatment of the signs and symptoms of DED by the US FDA in 2023 [14] and by Health Canada in 2024 (Table 2). In 2025, it was approved by the China National Medical Products Administration for the treatment of DED associated with MGD. For several years, PFHO has been marketed as a medical device in Europe, Australia, and New Zealand under the brand names EvoTears (URSAPHARM Arzneimittel, Saarbrücken, Germany) and NovaTears, including formulations with and without supplemental omega-3 [99,100].

Table 2. PFHO approvals across regions.

Brand name	Country	Approval	Indication
Miebo	US	Prescription medication in 2023	• Treatment of the signs and symptoms of DED
Miebo	Canada	Prescription medication in 2024	• Treatment of the signs and symptoms of DED
Heng Qin	China	Prescription medication in 2025	• Treatment of DED associated with MGD
EvoTears/NovaTears	Europe, Australia, and New Zealand	Medical device since 2015	• To relieve symptoms of dry eye • Formulations with and without omega-3

DED, dry eye disease; MGD, meibomian gland dysfunction; PFHO, perfluorohexyloctane.

11. Conclusion

Prior to the approval of PFHO ophthalmic solution in 2023, key limitations of some available DED medications included their slow onset of action and mechanisms of action restricted to increasing tear production and reducing inflammation. PFHO ophthalmic solution is the first FDA-approved eye drop for DED that directly targets tear evaporation. Following instillation, PFHO rapidly spreads across the ocular surface and forms a barrier at the air – tear film interface that inhibits evaporation of the tear film. Clinical trials in patients with DED and MGD have demonstrated significant improvement with PFHO versus saline in CFS and eye dryness symptoms, with significant improvement in DED symptoms observed as early as 5 minutes after dosing on day 1. PFHO was well tolerated in clinical trials, likely due to its lack of pH, absence of preservatives, and a refractive index similar to that of tears/water and, therefore, a low likelihood of causing visual disturbance on instillation. Thus, PFHO ophthalmic solution represents an important addition to the armamentarium of topical medications for DED, as it meets the previously unmet needs of rapid symptom relief and direct targeting of the evaporative component of disease.

12. Expert opinion

While excessive evaporation due to a dysfunctional lipid layer is the leading cause of DED, evaporation is central to all DED, since in aqueous-deficient DED, evaporation exceeds supply. The condition is compounded by lifestyle factors such as prolonged digital device use, which results in reduced and/or incomplete blinking. The prevalence of DED is increasing across age groups, including in the younger population [101]. For optimal outcomes, the latest guidelines from DEWS III focus on identifying and addressing the etiological driver(s) of the disease, with the goal of treatment being to restore homeostasis of the ocular surface [1]. While there are an increasing number of prescription therapeutics available for DED, PFHO is the only one that directly targets evaporation, the root cause of the majority of cases of dry eye.

PFHO has several unique physicochemical properties that make it ideally suited as an eye drop to treat evaporative DED. As a single-component, thermally and chemically stable, biologically inert, non-aqueous eye drop, the product is preservative-free and does not have a pH, an advantage over aqueous eye drops, for which such factors may cause stinging and irritation. PFHO does not scatter or absorb visible light; therefore, direct visual disturbance from PFHO on the surface of the eye is not expected, and minimal and transient effects on vision were confirmed in clinical trials. Additionally, PFHO is a liquid with very low surface tension and, thus, spreads well over the ocular surface, while its slow inherent rate of evaporation enables its long residence time at the ocular surface. In in vitro studies, unlike artificial tears, PFHO inhibited the rate of evaporation of saline and did so 4 times more than healthy human meibum. Studies in animals and humans demonstrate that PFHO can stabilize the underlying lipid and aqueous layers of the tear film and, thus, help restore ocular surface homeostasis [21,27,38,60–62].

Consistent with the above properties, PFHO treatment ameliorated both signs and symptoms of DED in multiple studies. Of note, and unlike other medications, PFHO was evaluated specifically in patients with MGD, consistent with its anti-evaporative mechanism of action. The clinical trial data for PFHO also stand out from that of other DED medications in that PFHO consistently reduced the primary symptom endpoint in 2 pivotal studies [69,70] and further provided rapid symptom relief over the first 2 weeks of treatment in an open-label, multicenter, phase 4 study [25]. In clinical trials, PFHO was very well tolerated, resulted in minimal adverse effects, and received high rates of patient satisfaction [25,65,69–72]. Early and lasting symptom relief and a favorable safety profile are 2 factors that can be impactful in a patient remaining compliant with therapy over the long term.

In the future, it would be beneficial to determine the efficacy of PFHO in comparison to (head-to-head studies) and in conjunction with other therapies, such as physical therapies, to improve Meibomian gland function and anti-inflammatory therapies. Evaluating PFHO in additional patient populations, such as younger adults (including assessing the impact of treatment on comfort of digital device use) and patients on glaucoma medications, can provide further information on the clinical utility of the medication.

In summary, PFHO is the only prescription medication that directly addresses the evaporative component of DED by mimicking the function of the TFLL to preserve a patient's natural tears. Its unique mechanism of action and physicochemical properties translate to consistent, rapid, and lasting reduction in symptoms of dry eye, healing of the ocular surface, and an excellent safety profile. Given that excessive tear evaporation due to MGD is the leading cause of DED, these attributes position PFHO as a beneficial first-line treatment option for patients suffering from this common condition.

Declaration of interest

MEC and JLV are employees of Bausch+Lomb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions statement

MEC: drafting the paper and revising it critically for intellectual content. JLV: drafting the paper and revising it critically for intellectual content. DB: conception, drafting the paper, and revising it critically for intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

Data availability statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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