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REVIEW

Differentiating Between Perfluorohexyloctane Ophthalmic Solution and Water-Free Cyclosporine Ophthalmic Solution 0.1% for Dry Eye Disease: A Review of Preclinical and Clinical Characteristics

Laura M. Periman · Darrell E. White · Douglas Katsev

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ABSTRACT

Perfluorohexyloctane ophthalmic solution (Miebo) and water-free cyclosporine ophthalmic solution 0.1% (Vevye) are recently approved treatments for dry eye disease (DED). Perfluorohexyloctane (PFHO) uses a novel approach to treat evaporative DED, whereas water-free cyclosporine (CsA 0.1%) is formulated to increase ocular delivery of its active ingredient to improve tear production. The two medications utilize the distinctive properties of two different semifluorinated alkanes (SFAs) to elicit their therapeutic effects. PFHO consists of 100% active ingredient and forms a monolayer on the surface of the tear film to inhibit evaporation. CsA 0.1% utilizes a vehicle consisting of perfluorobutylpentane (PFBP) and ethanol to facilitate delivery of cyclosporine to ocular tissues. The structure of these SFAs determines their differing behaviors and functions. The longer chain length of PFHO results in a slower evaporation rate and facilitates formation of a stable monolayer on the ocular surface. In vitro, PFHO demonstrated a substantially lower evaporation rate versus PFBP or human meibum, as well as a significantly longer ocular surface residence time. Ex vivo, PFHO demonstrated a longer ocular surface residence time than PFBP. The shorter chain length of PFBP enables it to better solubilize cyclosporine and improve drug delivery to ocular tissues. Although both of these ophthalmic drops utilize SFAs, their differences—in physicochemical properties and the mechanisms by which they are understood to intervene in the DED cycle—are important considerations in treatment selection for patients with DED.

Keywords: Anti-evaporative; Cyclosporine; Dry eye; Immunomodulator; Perfluorobutylpentane; Perfluorohexyloctane; Semifluorinated alkane

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Key Summary Points

Two water-free, preservative-free drops were recently approved by the US Food and Drug Administration for treatment of the signs and symptoms of dry eye disease (DED).

Perfluorohexyloctane ophthalmic solution (PFHO, Miebo) consists of 100% active ingredient, and water-free cyclosporine (CsA 0.1%, Vevye) utilizes a vehicle containing perfluorobutylpentane (PFBP).

Although both are semifluorinated alkanes (SFAs), PFHO and PFBP have distinctive physiochemical properties that lead to differences in behavior and function.

PFHO forms a stable monolayer on the ocular surface and slows tear film evaporation, whereas PFBP is used to better solubilize cyclosporine and improve drug delivery to ocular tissues.

PFHO may be an optimal SFA-based treatment for patients with evaporative DED, whereas CsA 0.1% may be more advantageous for patients with primarily aqueous-deficient DED.

INTRODUCTION

Dry eye disease (DED) is characterized by a loss of tear film homeostasis, resulting from insufficient tear production, excess evaporation, or both [1]. Excess tear film evaporation is implicated in up to 90% of all DED cases; approximately 30% of DED cases are due to a combination of aqueous deficiency and excess tear evaporation, whereas only 14% are due to aqueous deficiency alone [1–4]. Regardless of initial cause, loss of tear film homeostasis leads to a cycle of desiccation stress and friction at the ocular surface, resulting in tissue damage and inflammation, which then exacerbate stress on the ocular surface [1, 5]. Because DED operates as a cycle of stress, tissue damage, and inflammation, it is possible to address DED from multiple points in the disease process, whether it is excess evaporation, which is a leading driver of DED, or elsewhere in the cycle, such as tear production or ocular surface inflammation.

NOVEL APPROACHES TO THE COMPLEX PROBLEM OF DRY EYE DISEASE

Two water-free, preservative-free drops have recently been approved by the US Food and Drug Administration (FDA) for the treatment of the signs and symptoms of DED: perfluorohexyloctane ophthalmic solution (Miebo®; Bausch + Lomb) [6] and water-free cyclosporine ophthalmic solution 0.1% (Vevye®; Harrow Eye, LLC) [7]. Both perfluorohexyloctane (PFHO) and this formulation of cyclosporine (CsA 0.1%) obviate the need for an aqueous solvent, and therefore preservatives, by either consisting entirely of a semifluorinated alkane (SFA; PFHO) or including an SFA as a component of the formulation's vehicle (CsA 0.1%). SFAs are amphiphilic compounds with low surface tension that are both chemically inert and biocompatible [8]. Though both drugs contain an SFA, each plays a very different role in the formulation, with the physiochemical properties of each SFA helping facilitate the mechanisms of action for PFHO and CsA 0.1% (anti-evaporative vs. stimulating tear production, respectively), making them uniquely designed for their respective target DED patient populations [6, 7].

This review summarizes the preclinical and clinical characteristics of PFHO and CsA 0.1% to provide a comprehensive overview of how their respective physicochemical properties underpin their respective places in DED therapy. This article is based on previously conducted studies and does not contain any new studies performed by any of the authors on human participants or animals.

PFHO AND CSA 0.1%: TWO SFA-BASED DROPS, TWO VERY DIFFERENT DED TREATMENTS

SFAs are a class of molecules that are amphiphilic in nature as a result of their two different segments: a more polar fluorinated segment

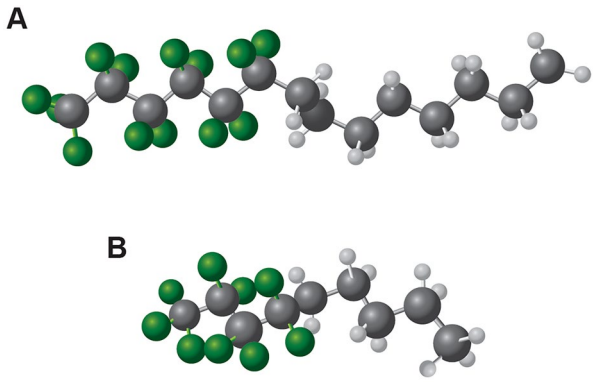

Fig. 1 Molecular structures of **a** perfluorohexyloctane (PFHO) and **b** perfluorobutylpentane (PFBP). Reproduced from Tsagogiorgas C, Otto M. Semifluorinated alkanes as new drug carriers—an overview of potential medical and clinical applications. Pharmaceutics. 2023;15:1211. https://doi.org/10.3390/pharmaceutics15041211 [13], under Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/)

and a lipophilic hydrocarbon segment [9]. The chain lengths of the respective segments give rise to substantially different physiochemical properties. Longer lengths of the fluorinated and hydrocarbon segments increase the intramolecular interactions between the two segments of the SFAs, decreasing their volatility (evaporation rate) [10, 11] and enabling them to form more stable monolayers at air–water interfaces [12].

As a DED therapy, PFHO ($C_{14}H_{17}F_{13}$ [F6H8]) is both the active ingredient and sole component, whereas CsA 0.1% contains perfluorobutylpentane ($C_9H_{11}F_9$ [F4H5]; PFBP) as part of the vehicle to deliver the active ingredient, cyclosporine, to ocular surface tissues (Fig. 1; Table 1) [6, 7, 13]. PFHO has longer fluorinated and hydrocarbon segments than PFBP, enabling it to form a stable monolayer at the air–water interface of the tear film [12]. Additionally, PFHO has a higher boiling point than PFBP and is less volatile, and thus evaporates more slowly, resulting in a longer ocular surface residence time [14, 15]. On the other hand, PFBP has a greater cyclosporine solubilization capacity and, although PFHO is retained longer on the ocular surface, PFBP appears to be the more suitable drug delivery

Table 1 Distinct properties and functions of PFHO and PFBP

	PFHO	**CsA 0.1%**
Active ingredient	PFHO 100%	CsA 0.1%
MOA	Anti-evaporative	Immunomodulation
Included SFA	PFHO	PFBP
Role of SFA in product	Active ingredient, anti-evaporative	Vehicle component (along with ethanol; enhances corneal bioavailability of active ingredient)
	PFHO	**PFBP**
Evaporation rate (in vitro gravimetric assay)	Slow (< 1.5% evaporated in 1 h)	Fast (93% evaporated in 1 h)
Corneal residence time (ex vivo model, % remaining)	54.5% (approx. 3 × more)	18.6%

Abbreviations: *CsA* cyclosporine, *MOA* mechanism of action, *PFBP* perfluorobutylpentane, *PFHO* perfluorohexyloctane, *SFA* semifluorinated alkane

Table created with data from Agarwal P, et al. *Int J Pharm*. 2018;538(1–2):119–129 [10]; Vittitow JL, et al. *Curr Ther Res Clin Exp*. 2023;98:100704 [9]; Miebo package insert. Bausch + Lomb; 2023 [6]; and Vevye package insert. Harrow, LLC; 2023 [7]

vehicle. The physiochemical properties of the individual SFAs in these two DED therapies—PFHO and, for CsA 0.1%, PFBP—therefore enable each therapy to achieve its respective goal: anti-evaporation for PFHO and, for CsA 0.1%, improved bioavailability of its active ingredient, the immunomodulator cyclosporine [10].

EVAPORATION RATES AND RESIDENCE TIME

The particular physiochemical properties of PFHO, with a lipophobic/aerophilic fluorinated segment and a lipophilic hydrocarbon segment, cause it to self-aggregate to form a well-organized monolayer at the air–tear film interface [9, 15]. PFHO has a greater inhibitory effect on the evaporation of saline than human meibum lipids in vitro [9] and demonstrated extended ocular surface residence time in a rabbit pharmacokinetic model [15].

An in vitro gravimetric analysis comparing the evaporation rate of PFHO directly with PFBP showed that < 1.5% of PFHO had evaporated at 1 h compared with 93% of PFBP, and < 50% of PFHO had evaporated at 24 h, the last studied timepoint, whereas PFBP had completely evaporated at 2 h (Fig. 2a) [10]. In an ex vivo model in porcine eyes, both PFHO and PFBP had significantly longer precorneal residence times than cyclosporine-containing DED drops, cyclosporine ophthalmic emulsion 0.05% (Restasis®; Allergan, Inc), or cyclosporine ophthalmic emulsion 0.1% (Ikervis®; Santen Pharmaceutical) (Fig. 2b) [10]. There was, however, a substantial (approximately threefold) difference between the two SFAs, with 54.5% of PFHO remaining on the corneal surface at 1 h versus 18.6% of PFBP [10]. Based on the observed lower evaporation rate and longer ocular surface residence time, these direct comparative data support the distinct anti-evaporative properties of PFHO.

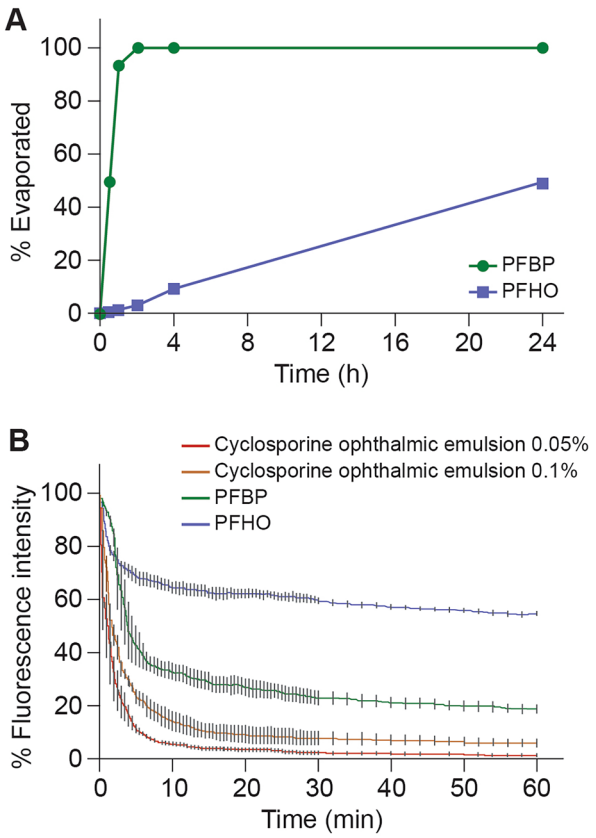

Fig. 2 Preclinical evaluations of perfluorohexyloctane (PFHO) and perfluorobutylpentane (PFBP). **a** In vitro percent evaporation rates over time. Evaporation rates were evaluated gravimetrically, adding 500 µL SFA to a preweighed tissue culture dish, and incubated at 35 ± 3 °C; the dish was then weighed again at each timepoint. **b** Ex vivo precorneal residence time measured by fluorescence intensity (0.05% w/v of fluorescent dye) of PFHO and PFBP vs. cyclosporine ophthalmic emulsion 0.05% and cyclosporine ophthalmic emulsion 0.1%. Fresh porcine corneas were incubated in a tissue culture dish at 35 ± 3 °C with a corneal sleeve placed on top. A peristaltic pump continuously perfused HBSS at a flow rate of 5.7 µL/min in and out of the dish, and 10 µL of each test formulation—each containing 0.05% w/v of fluorescent dye—was added. Fluorescence was then measured at each timepoint: every 30 s for the first 30 min, then every 2 min for up to 60 min. Note: The clinical significance of these data has not been established. Abbreviations: *HBSS* Hank's balanced salt solution, *PFBP* perfluorobutylpentane, *PFHO* perfluorohexyloctane, *SFA* semifluorinated alkane, *w/v* weight per volume. Figures reprinted with permission from Agarwal P, et al. *Int J Pharm*. 2018;538(1–2):119–129 [10]

SOLUBILIZATION OF CYCLOSPORINE

In contrast to PFHO, the active ingredient in the PFBP-based DED drop (CsA 0.1%) is the immunomodulator cyclosporine; PFBP, along with ethanol, acts as the vehicle [7]. Thus, the mechanism of action for CsA 0.1% is mediated via the ability of cyclosporine to inhibit calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells, resulting in an increase in tear production (Table 1) [7]. However, cyclosporine has poor water solubility, which has historically made it difficult to formulate for topical ocular use [16]. In an ex vivo, whole-eye model in rabbits, both PFHO and PFBP facilitated delivery of cyclosporine to the cornea, but PFBP had better solubilization capacity of cyclosporine (Fig. 3) [10]. Although PFHO better enabled corneal penetration of cyclosporine at a 0.05% concentration than did PFBP, PFHO had less capacity to solubilize the higher 0.1% concentration of cyclosporine used in the PFBP-based drop. Thus, PFBP was selected for use as a vehicle component in the ultimate formulation of CsA 0.1%. Of note, a pharmacokinetics study in rabbits found that an 11-µL drop of CsA 0.1% and a 50-µL drop of cyclosporine ophthalmic emulsion 0.1%, an oil-based emulsion indicated for DED, have similar degrees of cyclosporine penetration in the cornea, conjunctiva, and lacrimal glands after topical ocular administration [17]. Therefore, similar anterior ocular tissue levels of the active ingredient could be delivered to the target tissues with the use of the PFBP vehicle as compared to the emulsion formulation, despite the much smaller drop size.

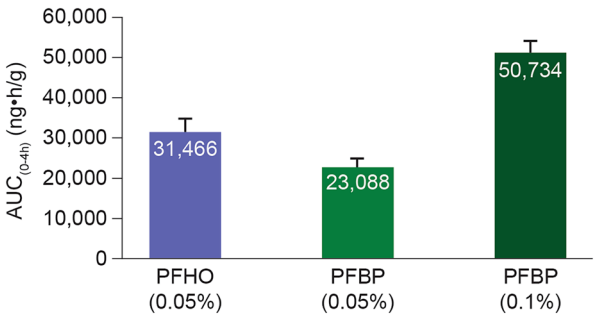

Fig. 3 Corneal penetration at 4 h of CsA solubilized in PFHO (0.05%) or PFBP (0.05% or 0.1%) from the test formulations ($n = 3$ for each). Amount of CsA (ng) per gram of corneal tissue following a 50-µL dose of test solution. Error bars represent the SEM. Note: PFHO (0.1%) was not included in the analysis as a result of difficulty solubilizing CsA 0.1%. There was no statistical analysis provided for the comparison of PFHO (0.05%) vs. PFBP (0.1%). The clinical significance of these data has not been established. Abbreviations: $AUC_{(0-4h)}$ area under the curve from 0 to 4 h, *CsA* cyclosporine, *PFBP* perfluorobutylpentane, *PFHO* perfluorohexyloctane, *SEM* standard error of the mean. Figure created with data from Agarwal P, et al. *Int J Pharm*. 2018;538(1–2):119–129 [10]

PFHO AND CSA 0.1% PHASE 3 CLINICAL STUDIES

PFHO and CsA 0.1% have not been compared head-to-head in clinical studies, but both have been examined individually in multiple randomized, controlled clinical studies that assessed their efficacy and safety for the treatment of DED. The PFHO phase 3 program included the pivotal GOBI (NCT04139798; $N = 597$) and MOJAVE (NCT04567329; $N = 620$) studies in US adult patients with DED associated with Meibomian gland dysfunction (MGD) [18, 19]. Both studies randomized patients 1:1 to treatment with PFHO or hypotonic saline four times per day (QID). Additionally, the KALAHARI study (NCT04140227) assessed the long-term clinical efficacy and safety of PFHO through 52 weeks in 208 patients from the GOBI study [20].

CsA 0.1% was evaluated in the pivotal ESSENCE-1 (phase 2B/3; NCT03292809; $N = 328$) and ESSENCE-2 studies (phase 3; NCT04523129; $N = 834$) and a phase 3 study parallel to ESSENCE-2 conducted in 206 Chinese patients (NCT05841043) [21–23]. Following a 14-day artificial tear run-in period, patients were randomized 1:1 to treatment with CsA 0.1% or its vehicle twice per day (BID). Unlike the PFHO clinical studies, the presence of MGD was an exclusion criterion in the CsA 0.1% pivotal studies. Additionally, patients in CsA 0.1% studies typically had more severe DED signs: baseline mean total corneal fluorescein staining (tCFS)

scores by treatment group were nearly twofold higher in CsA 0.1% studies than PFHO clinical studies (CsA 0.1% studies, 11.5–12.3; PFHO studies, 6.7–7.1), and average baseline Schirmer test scores by treatment group were nearly 8 points lower in CsA 0.1% studies than PFHO studies (CsA 0.1% studies, 3.6–5.2; PFHO studies, 11.7–12.8) [18, 19, 21–23]. Therefore, consistent with their respective mechanisms of action (tear stimulator vs. anti-evaporative), in the CsA 0.1% trials, all patients had aqueous deficient DED (Schirmer score inclusion criteria of ≥ 1 and ≤ 10 mm) and severe corneal staining (tCFS ≥ 10 on the 0–15 National Eye Institute [NEI] scale), while in the PFHO studies all patients had evaporative DED (MGD score of ≥ 3 on a 0–15 scale, tCFS 4–11 on the NEI scale, and Schirmer score ≥ 5 mm).

Efficacy in PFHO and CsA 0.1% Phase 3 Clinical Studies

The GOBI and MOJAVE studies consistently met both of their primary efficacy endpoints: PFHO provided significant improvements in tCFS and visual analog scale (VAS) eye dryness score versus saline control at day 57 ($P < 0.001$ for each; Table 2) [18, 19]. The ESSENCE-1 and ESSENCE-2 studies also met the primary sign endpoint: at 4 weeks, CsA 0.1% significantly improved tCFS versus vehicle (ESSENCE-1, $P = 0.0002$; ESSENCE-2, $P = 0.03$; Table 2) [21]. In addition, in the study by Peng et al., which replicated ESSENCE-2 in a Chinese population, CsA 0.1% significantly improved tCFS versus vehicle at week 4 ($P < 0.001$) [23]. However, CsA 0.1% did not significantly increase tear production versus vehicle as measured by Schirmer test in ESSENCE-1 [21], and Schirmer test scores were not reported for ESSENCE-2 [22], nor was the primary symptom endpoint met in any of the studies [21–23]. In GOBI and MOJAVE, DED signs and symptoms were improved at day 15, with significant reductions in tCFS and VAS eye dryness scores. The ESSENCE-1 and ESSENCE-2 studies both met their primary DED sign endpoint: at 4 weeks, CsA 0.1% significantly improved tCFS change from baseline versus vehicle (ESSENCE-1, $P = 0.0002$; ESSENCE-2, $P = 0.03$; Table 2). In ESSENCE-1, the primary symptom endpoint of total Ocular Surface Disease Index score was not significantly improved with CsA 0.1% versus vehicle [21], and in ESSENCE-2 [22] and the study by Peng et al. [23], CsA 0.1% did not significantly improve the primary symptom endpoint, eye dryness score, versus vehicle (the same primary endpoint as the PFHO pivotal studies).

In terms of onset of action, in GOBI and MOJAVE, DED signs and symptoms were improved with PFHO at day 15, with significant reductions in both tCFS and VAS eye dryness scores [18, 19]. In the three CsA 0.1% studies, a significantly greater reduction versus vehicle was evident at day 15 for tCFS but not symptoms [21–23]. Sustained efficacy in terms of reduction from baseline was demonstrated for both drugs for both signs and symptoms. Patients treated with PFHO who proceeded from GOBI to the open-label, long-term extension KALAHARI study continued to demonstrate significant reductions from baseline in tCFS and VAS eye dryness scores through week 52 [20]. Patients in the saline crossover to PFHO group in KALAHARI demonstrated improvements in tCFS and VAS eye dryness scores at 4 weeks after initiating PFHO, which were maintained through week 52. In the ESSENCE-2 open-label extension (OLE) study in which patients received CsA 0.1% for 52 weeks, there were statistically significant improvements from ESSENCE-2 baseline in both tCFS and eye dryness score at week 4, which were sustained through week 52, with a more pronounced improvement from OLE baseline at week 4 for tCFS than for eye dryness score in the patients who switched to CsA 0.1% [24].

Safety in PFHO and CsA 0.1% Clinical Studies

In the GOBI, MOJAVE, and KALAHARI studies of PFHO, most adverse events (AEs) were mild or moderate in severity; there were no serious ocular AEs, and discontinuation rates were low [18–20]. In GOBI, the most common ocular AE in the PFHO group was blurred vision (3.0%) [18]; in MOJAVE, the most common ocular AE in the PFHO group was blepharitis (1.6%) [19]. The

Table 2 Efficacy results from key PFHO and CsA 0.1% phase 3 clinical study programs

PFHO					CsA 0.1%				
Pivotal studies	Sign endpoints*		Symptom endpoints†		Pivotal studies	Sign endpoints*		Symptom endpoints†	
		LS mean between-group difference in CFB		LS mean between-group difference in CFB			LS mean between-group difference in CFB		LS mean between-group difference in CFB
GOBI [18] PFHO QID ($n = 303$) Hypotonic saline QID ($n = 294$) Mean baseline scores: PFHO; saline: tCFS = 6.7; 6.7 EDS = 66.5; 66.8	tCFS at 57 days (primary) tCFS at 15 days (key secondary)	− 0.97 $P < 0.001$ − 0.6 $P = 0.001$	EDS at 57 days (primary) EDS at 15 days (key secondary)	− 7.6 $P < 0.001$ − 4.7 $P = 0.009$	**ESSENCE-1** [21] CsA 0.1% BID ($n = 162$) Vehicle BID ($n = 166$) Mean baseline scores: CsA 0.1%; vehicle tCFS = 11.5; 11.5 EDS = 68.5; 69.9	tCFS at 29 days (primary)	− 0.8 $P = 0.0002$	Total OSDI score at 29 days (primary)	Not reported $P = 0.26$
MOJAVE [19] PFHO QID ($n = 311$) Hypotonic saline QID ($n = 309$) Mean baseline scores: PFHO; saline tCFS = 7.0; 7.1 EDS = 64.7; 64.3	tCFS at 57 days (primary) tCFS at 15 days (key secondary)	− 1.2 $P < 0.001$ − 0.6 $P = 0.001$	EDS at 57 days (primary) EDS at 15 days (key secondary)	− 10.2 $P < 0.001$ − 7.8 $P < 0.001$	**ESSENCE-2** [22] CsA 0.1% BID ($n = 423$) Vehicle BID ($n = 411$) Mean baseline scores: CsA 0.1%; vehicle tCFS = 11.5; 11.5 EDS = 70.4; 70.0	tCFS at 29 days (primary)	− 0.4 $P = 0.03$	EDS at 29 days (primary)	1.4 $P = 0.38$

Table 2 continued

PFHO					CsA 0.1%				
Pivotal studies	Sign endpoints*		Symptom endpoints†		Pivotal studies	Sign endpoints*		Symptom endpoints†	
		LS mean between-group difference in CFB		LS mean between-group difference in CFB			LS mean between-group difference in CFB		LS mean between-group difference in CFB
Open-label extension study		**Mean (SD) CFB**		**Mean (SD) CFB**	**Open-label extension study**		**Mean (SD) CFB**		**Mean (SD) CFB**
KALAHARI [20] Extension study from GOBI PFHO QID ($n = 208$)	tCFS at week 52	− 2.1 (2.5)	EDS at week 52	− 33.7 (28.6)	ESSENCE-OLE [24] Extension study from ESSENCE-2 CsA 0.1% BID ($n = 202$)	tCFS at week 52	− 5.6 (3.2)	EDS at week 52	− 25.4 (26.4)

Abbreviations: *BID* twice per day, *CFB* change from baseline, *CsA* cyclosporine, *EDS* eye dryness score, *LS* least-squares, *OSDI* Ocular Surface, Disease Index, *PFHO* perfluorohexyloctane, *QID* 4 times per day, *SD* standard deviation, *tCFS* total corneal fluorescein staining, *VAS* visual analog scale

*Fluorescein staining of five areas of the cornea (inferior, superior, central, nasal, and temporal) rated by the investigator using the National Eye Institute scale from grade 0 (no staining) to grade 3 (heavy staining); tCFS score was the sum of the individual scores (maximum of 15)

†EDS rated on a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort)

most common ocular AEs in KALAHARI (occurring in ≥ 2 patients) were vitreous detachment (1.9%; none considered related to study treatment), allergic conjunctivitis (1.4%), blurred vision (1.4%), and increased lacrimation (1.4%) [20]. There was one severe AE of eye irritation in GOBI that led to treatment discontinuation [18], and in KALAHARI, there was one severe AE of bilateral eyelid irritation, which the investigator considered possibly related to PFHO, but which did not result in discontinuation [20].

Across its clinical studies, CsA 0.1% demonstrated a favorable safety profile [21–23]. All three vehicle-controlled studies examining CsA 0.1%—ESSENCE-1, ESSENCE-2, and the study by Peng et al.—reported that AE rates were comparable between CsA 0.1% and control groups, and ocular AEs were largely mild-to-moderate in intensity. In both ESSENCE studies, the most common ocular AEs were reduced visual acuity (ESSENCE-1, 3.1%; ESSENCE-2, 1.7%), blurred vision (ESSENCE-1, 1.2%; ESSENCE-2, 0.5%), and instillation site pain or reactions (ESSENCE-1, 2.5%; ESSENCE-2, 10.2%) [21, 22]. Similar to what was observed in ESSENCE-2, the study by Peng et al. also reported common (> 2%) ocular AEs of reduced visual acuity (12.6%), ocular discomfort (3.9%), eye pain (2.9%), blurred vision (2.9%), and installation site reactions (2.9%) [23]. Few serious treatment-emergent AEs were reported in either ESSENCE-1 or ESSENCE-2 and none were considered related to the study drug [21, 22]. No severe ocular AEs were reported in ESSENCE-1, ESSENCE-2, or the study by Peng et al. [22, 23]. In the ESSENCE-OLE study, the most common AE was mild instillation site pain (6.5%); other AEs occurring at an incidence ≥ 2% included vitreous detachment (4.5%), reduced visual acuity (3.0%), and posterior capsule opacification (1.5%) [24]. One patient discontinued as a result of an ocular AE (mild ocular burning on instillation) [24].

CLINICAL CONTEXT

The longer chain length of the PFHO molecule makes PFHO especially well suited for inhibiting tear film evaporation, a pathophysiological process that is a key factor in the development and progression of the majority of DED cases [1, 9, 10]. PFBP, on the other hand, has a shorter chain length and evaporates more rapidly, but is better able to solubilize a 0.1% concentration of cyclosporine, an established treatment targeting low tear production in DED [7, 10].

Accordingly, these differences appear to translate to different clinical outcomes in the respective pivotal trials, which target two distinct patient populations. In the case of PFHO, study participants had predominantly evaporative dry eye, while in the CsA 0.1% studies, participants had aqueous-deficient DED with severe tCFS. PFHO and CsA 0.1% both demonstrated significant improvement in corneal staining, but only PFHO met its primary symptom endpoints, significantly improving VAS eye dryness scores among users [18–23]. Although the immunomodulatory and anti-inflammatory effects of cyclosporine have historically been used to increase tear production in patients with aqueous-deficient DED [25], CsA 0.1% did not significantly increase tear production in ESSENCE-1, nor did it improve patient symptoms as measured by VAS eye dryness score in ESSENCE-2 [21, 22].

In clinical practice, we benefit from the continued proliferation of treatments to manage the complex, multifactorial condition that is DED. When considering how to best apply SFA-based therapies for DED, it is important for us to understand what makes each distinct in order to provide the best treatment for our patients. For example, PFHO has demonstrated reduction in both signs and symptoms of DED in patients with DED and MGD, whereas CsA 0.1% has demonstrated reduction in ocular surface damage in patients with aqueous-deficient DED (including those with very low Schirmer test scores). PFHO may be an optimal SFA-based treatment for patients with evaporative DED, whereas CsA 0.1% may be more advantageous for patients with primarily aqueous-deficient DED.

CONCLUSIONS

PFHO and CsA 0.1% are both FDA-approved therapies for the treatment of DED, and the inclusion of SFAs makes them distinct from other topical formulations: they are both water- and preservative-free. Although their similarities may prompt clinicians to group PFHO and CSA 0.1% together, their differences—in physicochemical properties and the mechanisms by which they are understood to intervene in the DED cycle—are notable and important to consider.

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Declarations

Conflict of Interest. Laura M. Periman reports serving on advisory boards, speakers bureaus, and/or as a consultant for Alcon, Aldeyra Therapeutics, Allergan, Amgen, Azura Ophthalmics, Bausch + Lomb, Bruder Healthcare, Dompé, Eyedetec Medical, Kala Pharmaceuticals, Lumenis Be, Mallinckrodt, Myze, Novartis Pharmaceuticals, Nusight Medical, Olympic Ophthalmics, Science Based Health, Scope Health, Sun Pharmaceutical Industries, Tarsus, ThermaMEDx, Verséa, Visant, and Viatris; serving as a principal investigator for Alcon, Bausch + Lomb, Kala Pharmaceuticals, Lumenis Be, Novartis Pharmaceuticals, Olympic Ophthalmics, Tarsus, and Viatris; and is a shareholder of Eyedetec Medical, Myze, Quench Method, ThermaMEDx, Verséa, and Visant. Darrell E. White reports serving as a consultant and speaker to Bausch + Lomb. Douglas Katsev reports serving as a consultant and speaker to Bausch + Lomb. Douglas Katsev has no financial interest in the subject matter of this manuscript. The authors report no other conflicts of interest in this work.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies performed by any of the authors on human participants or animals.

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