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ORIGINAL RESEARCH

Early Effects of Perfluorohexyloctane Ophthalmic Solution on Patient-Reported Outcomes in Dry Eye Disease: A Prospective, Open-Label, Multicenter Study

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Early Effects of Perfluorohexyloctane Ophthalmic Solution on Patient-Reported Outcomes in Dry Eye Disease: A Prospective, Open-Label, Multicenter Study

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ABSTRACT

***Introduction*:** Perfluorohexyloctane ophthalmic solution (PFHO) is indicated for the treatment of signs and symptoms of dry eye disease (DED) and targets excessive tear evaporation. This study evaluated patient-reported outcomes early in treatment with PFHO.

***Methods*:** This prospective, multicenter, open-label, phase 4 study enrolled adults with a history of DED for ≥6 months. PFHO was instilled in both eyes four times daily for 14 days. Patients completed early outcome surveys during four clinic visits (day 1 [pretreatment; 5 and 60 min post-PFHO instillation] and days 3, 7, and 14). Symptom severity, symptom frequency, and treatment satisfaction were rated on visual analog scales (range 0–100). The primary endpoint was mean change from baseline in overall DED symptom severity at day 7. Secondary endpoints included change in severity of individual DED symptoms (eye dryness, blurred vision, eye irritation, light sensitivity, eye tiredness, burning/stinging, eye itching, eye pain); change in frequency (measured as percentage of time experienced) of the most bothersome symptom, awareness of dry eye symptoms, and fluctuation in quality of vision; and treatment satisfaction.

***Results*:** Ninety-nine patients enrolled (85.9% female; age range 35–81 years). The primary endpoint was met: mean (SD) overall symptom severity decreased significantly from 72.1 (17.0) at baseline to 27.8 (22.3) at day 7 (mean change, −44.5; $P<0.0001$). Mean (SD) percentage of time

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experiencing the most bothersome symptom decreased from 77.9% at baseline to 34.7% at day 14 ($P<0.0001$). Significant reductions in severity and frequency also were observed for all symptoms at all postbaseline assessments ($P<0.0001$). Median ratings of treatment satisfaction were 83.0 at day 3, 86.0 at day 7, and 90.0 at day 14.

Conclusion: Early in the course of treatment with PFHO, patients with DED experienced significant reductions in dry eye symptom frequency and severity. Treatment satisfaction with PFHO was high.

Trial Registration: ClinicalTrials.gov identifier NCT06309953.

Keywords: Dry eye; Patient-reported outcomes; Perfluorohexyloctane; Symptoms

Key Summary Points

Why carry out this study?

In randomized controlled trials of perfluorohexyloctane ophthalmic solution (PFHO), significant reductions in signs and symptoms of dry eye disease were observed beginning at day 15 (the first postbaseline assessment) for PFHO compared with a hypotonic saline control.

This prospective, multicenter, open-label study evaluated patient-reported outcomes (symptom severity, symptom frequency, treatment satisfaction) during the first 14 days of PFHO treatment.

What was learned from this study?

Statistically significant and clinically meaningful reductions in the severity and frequency of dry eye disease (DED) symptoms were observed as early as the third day of treatment with PFHO.

PFHO also provided immediate symptom relief after a single instillation (5 min and 60 min post-dose).

Identification of the most bothersome DED symptom enabled patient-specific assessment of treatment effectiveness.

INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder of the ocular surface characterized by a loss of tear film homeostasis [1]. DED can be broadly categorized as aqueous deficient, in which decreased lacrimation leads to a reduction in the aqueous component of the tear film, or evaporative, in which deficiencies in the tear-film lipid layer quality and/or quantity (most commonly caused by Meibomian gland dysfunction [MGD]) result in increased tear evaporation [1–3]; however, etiology is mixed in many patients [4]. A loss of tear film homeostasis leads to a cycle of DED pathophysiology, which includes tear hyperosmolarity, inflammation, goblet cell loss, and epithelial cell apoptosis [2, 5]. Resulting DED symptoms (e.g., eye dryness, burning/stinging, foreign body sensation, light sensitivity, blurred vision) can negatively affect quality of life, work productivity, and leisure activities [6, 7]. DED is often progressive, and patients who do not experience adequate relief from home-based therapies (e.g., lid hygiene, warm compresses, over-the-counter lubricating eye drops) often require additional treatment [8].

Perfluorohexyloctane ophthalmic solution (PFHO) is a water-free, preservative-free, topical ophthalmic medication approved by the US Food and Drug Administration (FDA) for treatment of the signs and symptoms of DED (Miebo®; Bausch + Lomb, USA) [9, 10]. PFHO is an amphiphilic molecule consisting of an aerophilic fluorinated segment and a lipophilic hydrocarbon segment [11, 12]. Because of its unique structure, PFHO spreads rapidly across the ocular surface and forms a long-lasting barrier at the air–tear film interface, which inhibits tear evaporation [11, 13]. In randomized controlled trials (RCTs) in patients with DED and clinical signs of MGD, PFHO was superior to a hypotonic saline control for reducing both the signs and symptoms of DED [14–16]. Improvements observed after 8 weeks of treatment were sustained in a year-long open-label extension study [17].

In clinical trials of PFHO, day 15 was the first postbaseline timepoint at which signs and symptoms of DED were assessed [14–16]. The aim of this postmarketing study was to evaluate

patient-reported outcomes during the first 2 weeks of treatment with PFHO.

METHODS

Study Design

This prospective, open-label, phase 4 study (NCT06309953) was conducted from February 2024 through June 2024 at six sites in the USA. The study was conducted in accordance with the Good Clinical Practice guideline of the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. The study protocol was approved by a central institutional review board (Advarra IRB; Columbia, MD; IRB Registration number 00000971). All patients provided written informed consent before initiation of any study-related procedures.

Patients

Eligible patients were adults (≥ 18 years of age) who met the following key inclusion criteria in ≥ 1 eye (the same eye): self-reported history of DED for ≥ 6 months, Ocular Surface Disease Index (OSDI) score ≥ 25, total corneal fluorescein staining (tCFS) score ≥ 4 and ≤ 11 (National Eye Institute scale; range 0–15), tear film breakup time (TFBUT) ≤ 5 s, total MGD score ≥ 3 (range 0–15), and Schirmer I test (without anesthesia) ≥ 5 mm.

Patients were excluded from participation if they had clinically significant slit-lamp findings or abnormal lid anatomic features (including eye trauma, history of Stevens-Johnson syndrome, active blepharitis or lid margin inflammation, ocular or periocular rosacea, or DED secondary to scarring), active ocular allergies, an ocular or systemic infection, or best-corrected visual acuity (BCVA) of 0.7 logarithm of the minimum angle of resolution or worse as assessed using a Snellen chart. Patients also were excluded if they had been treated with prescription dry eye therapy, topical ocular steroids, topical antiglaucoma medications, LipiFlow (Johnson & Johnson Vision Care, Inc), intense pulse light, or other procedures affecting the Meibomian glands within the previous 6 months; had undergone intraocular surgery or ocular laser surgery within 3 months or refractive surgery within 2 years; or had received or removed a permanent punctum plug within 3 months (6 months for dissolvable plugs). Contact lens use was prohibited within the month prior to enrollment and throughout the study. Use of any eye drops (including artificial tears) or an intranasal tear neurostimulator was prohibited within the 24 h prior to enrollment and throughout the study. Patients with any prior use of PFHO eye drops were excluded.

Procedures

Patients instilled PFHO eye drops in both eyes four times daily for 14 days, consistent with the US prescribing information. An early outcomes survey assessed patient-reported symptom severity, symptom frequency, and treatment satisfaction. Surveys were completed on day 1 (predose [baseline] and at 5 min and 60 min after the first instillation of PFHO) and on days 3, 7, and 14 (within 30 min to 4 h postdose). Patients rated the severity of overall dry eye symptoms and eight specific symptoms (eye dryness, burning/stinging, eye itching, light sensitivity, eye pain, eye tiredness, eye irritation, and blurred vision) on a visual analog scale (VAS) from 0 (none) to 100 (worst severity possible). At baseline, each patient identified their most bothersome symptom. Symptom frequency was assessed (at all timepoints except post-instillation on day 1) as the percentage of time that patients experienced their most bothersome symptom, awareness of dry eye symptoms, and fluctuations in quality of vision, each rated on a VAS from 0% (never) to 100% (all the time). Treatment satisfaction was rated on a VAS from 0 (extremely dissatisfied) to 100 (extremely satisfied). At the 5-min postdosing assessment on day 1, patients selected up to three of the following terms to describe how PFHO felt when placed in the eyes: burning, cooling, grainy, irritating, no sensation, refreshing, silky, smooth, soothing, and stinging. The OSDI, a 12-item questionnaire with three components (symptom severity, impact on daily activities, environmental triggers) [18, 19], was completed at baseline and day 14. Treatment

compliance was assessed by review of dosing diaries and computed as the number of doses administered divided by the number of doses expected.

Statistical Analysis

The primary endpoint was change from baseline in the severity of overall dry eye symptoms at day 7. Secondary endpoints included change in overall symptom severity at other timepoints, change in the severity of individual symptoms, change in symptom frequency, change in OSDI score, and treatment satisfaction.

It was estimated that a sample size of 100 patients would provide 80% power to detect a difference of 8.2 in the mean score on the primary endpoint at baseline versus day 7, assuming a standard deviation of differences of 25 and a dropout rate of 25%, using a paired *t* test with two-sided alpha = 0.05. Data were summarized using descriptive statistics. For measures of effectiveness, change from baseline at each postbaseline assessment was analyzed using a paired *t* test with two-sided alpha = 0.05. No adjustments were made for multiplicity.

RESULTS

Patients

A total of 115 patients were screened, of whom 16 were excluded (14 did not meet all inclusion

Table 1 Patient demographics and baseline characteristics

		Patients (*n* = 99)
Age, years		
Mean (SD)		61.3 (11.8)
Age group, *n* (%)		
< 65 years		56 (56.6)
≥ 65 years		43 (43.4)
Sex, *n* (%)		
Female		85 (85.9)
Male		14 (14.1)
Race, *n* (%)		
White		90 (90.9)
Black or African American		7 (7.1)
Asian		2 (2.0)
OSDI total score, mean (SD)		50.5 (16.7)
	OD	**OS**
TFBUT, mean (SD), seconds	3.6 (0.8)	3.5 (0.8)
tCFS score, mean (SD)	5.3 (1.3)	5.1 (1.4)
MGD score, mean (SD)	8.3 (2.5)	8.2 (2.7)
Schirmer I test, mean (SD), mm	14.7 (10.8)	13.6 (10.3)

MGD Meibomian gland dysfunction, *OSDI* Ocular Surface Disease Index, *SD* standard deviation, *TFBUT* tear film breakup time, *tCFS* total corneal fluorescein staining

criteria, and 2 met exclusion criteria for recently receiving prohibited ocular therapy). Ninety-nine patients were enrolled and treated with PFHO (full analysis set). Patients were primarily female (85.9%) and white (90.9%); age ranged from 35 to 81 years (Table 1). Ninety-eight patients (99.0%) completed the study; one patient withdrew early (patient decision). Treatment compliance was between 90% and 120% of expected doses for 97 patients (98.0%). At baseline, eye dryness was identified as the most bothersome symptom by 28.3% of patients, followed by blurred vision (17.2%), eye irritation (14.1%), light sensitivity (13.1%), eye tiredness (12.1%), burning/stinging (11.1%), eye itching (4.0%), and eye pain (0.0%).

Effectiveness

The mean (SD) score on the VAS for overall dry eye symptoms was 72.1 (17.0) at baseline and decreased to 38.5 (22.8) at 5 min post-instillation, 31.7 (22.1) at 60 min post-instillation, 33.2 (25.1) at day 3, 27.8 (22.3) at day 7 (primary endpoint), and 24.7 (23.0) at day 14 (Fig. 1). The primary endpoint was met: mean (SD) change from baseline at day 7 was −44.5 (25.2); $P<0.0001$. A similar pattern in severity reduction was observed for each individual dry eye symptom (Fig. 2; $P<0.0001$ for change from baseline on all item scores at all timepoints). Across items, percent reduction from baseline severity ranged from 27% to 53% at 5 min post-instillation on day 1, 50–69% at 60 min post-instillation on day 1, 50–59% at day 3, 59–71% at day 7, and 62–75% at day 14.

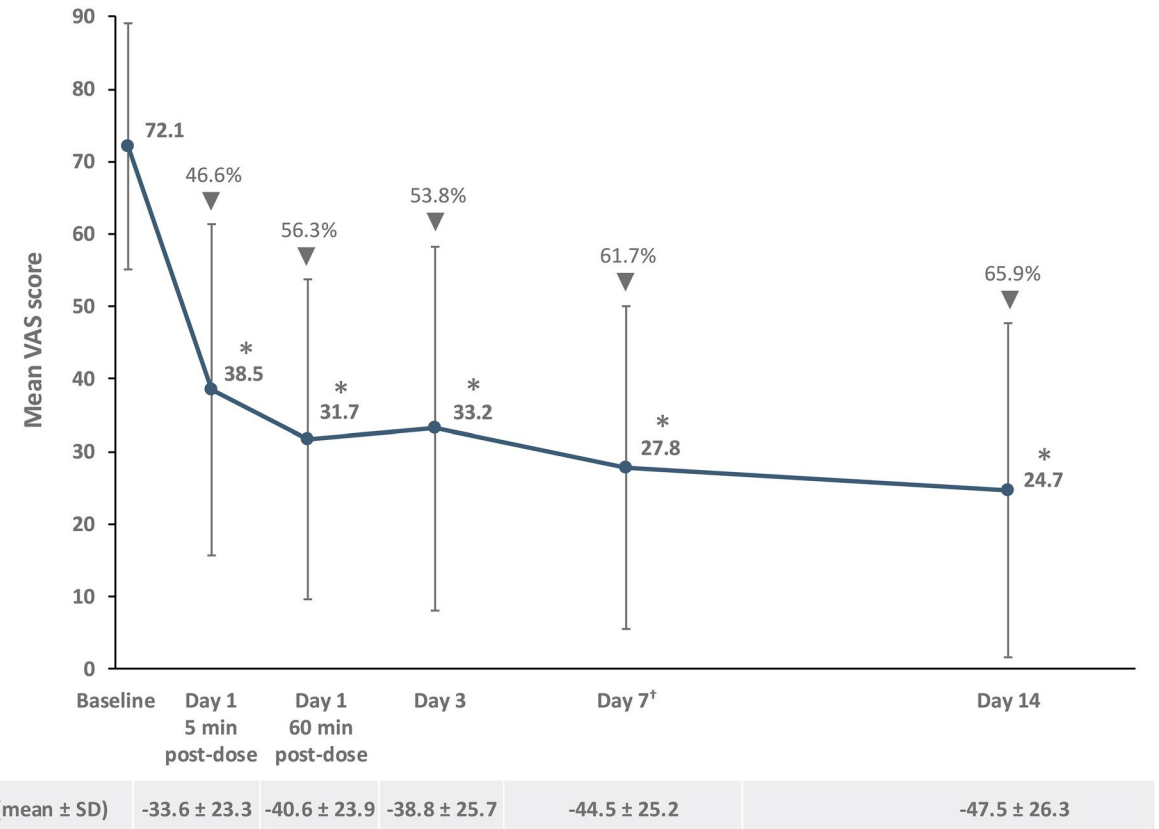

Fig. 1 Patient-reported severity of overall dry eye symptoms. Error bars represent SD. Data missing for one patient at day 1 (60 min post-dose assessment; item left blank), and one patient at days 7 and 14 (due to study discontinuation). *$P<0.0001$ versus baseline (paired t test). †Primary endpoint. *CFB* change from baseline, *SD* standard deviation, *VAS* visual analog scale

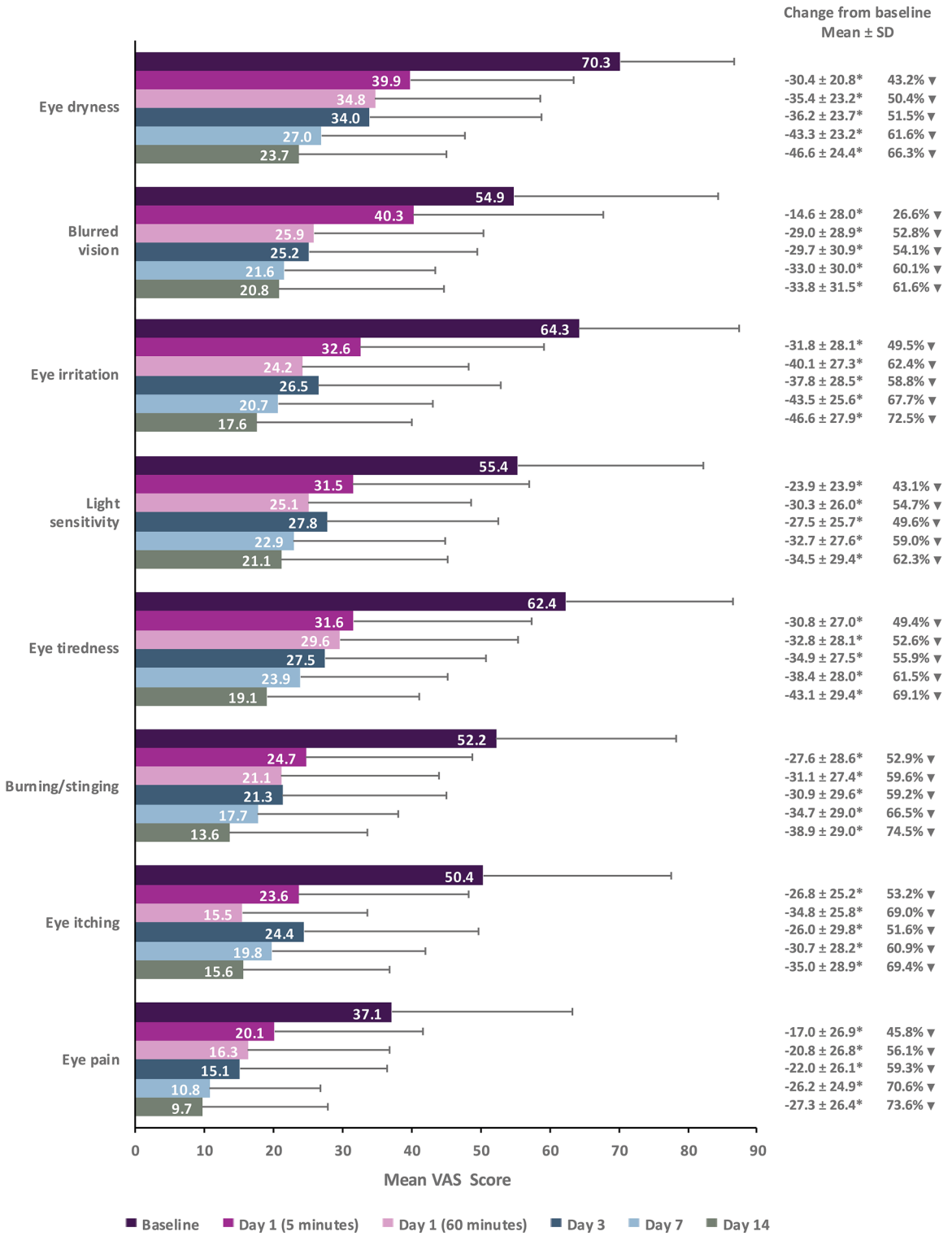

Fig. 2 Patient-reported severity of individual dry eye symptoms. Error bars represent SD. Data missing for one patient at days 7 and 14 (due to study discontinuation). *$P < 0.0001$ versus baseline (paired t test). *SD* standard deviation, *VAS* visual analog scale

Mean frequency (percentage of time) experiencing the most bothersome symptom decreased significantly from 77.9% at baseline to 46.7% at day 3, 41.3% at day 7, and 34.7% at day 14 (Fig. 3; all $P<0.0001$). Significant decreases were also observed in mean frequency of awareness of dry eye symptoms (77.6% at baseline, 39.7% at day 3, 32.6% at day 7, 27.6% at day 14; all $P<0.0001$) and fluctuations in quality of vision (62.8% at baseline, 29.8% at day 3, 24.5% at day 7, 19.4% at day 14; all $P<0.0001$).

Mean OSDI total score and subtotal scores (ocular symptoms, vision-related function, environmental triggers) were decreased significantly from baseline at day 14 (Table 2). Median VAS ratings of treatment satisfaction were 75.0 at 5 min post-instillation on day 1, 84.0 at 60 min post-instillation on day 1, 83.0 at day 3, 86.0 at day 7, and 90.0 at day 14. The percentage of patients who selected each descriptor for how the study treatment felt were 68.7% silky, 67.7% smooth, 65.7% soothing, 24.2% refreshing, 16.2% cooling, 9.1% no sensation, 6.1% stinging, 4.0% irritating, 2.0% grainy, and 2.0% burning.

Safety

One adverse event was reported. One patient experienced eye pain (in the right eye) that was moderate in severity and judged by the investigator as not serious and not related to study medication. The event resolved after oral administration of ibuprofen. Mean (SD) change from baseline at day 14 in BCVA (measured as logMAR) was −0.01 (0.08) in the right eye and −0.02 (0.07) in the left eye. The proportion of patients with BCVA of 20/20 or better was 53.5% at baseline and 59.2% at day 14 in the right eye, and 54.5% and 60.2%, respectively, in the left eye. The proportion of patients with BCVA of 20/40 or better was 99.0% at baseline and 100% at day 14 in the right eye, and 98.0% and 99.0%, respectively, in the left eye.

DISCUSSION

This multicenter, open-label, postmarketing study evaluated early treatment outcomes and found that PFHO provided symptom relief during the first 2 weeks of treatment, with notable symptom reduction as soon as 5 min and

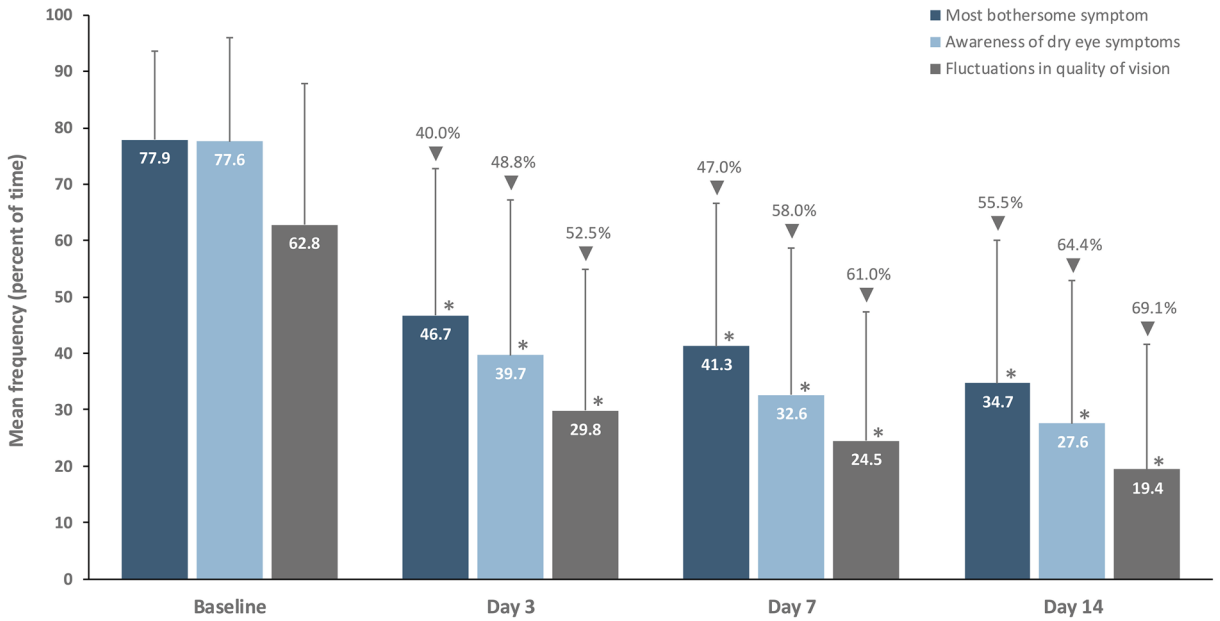

Fig. 3 Patient-reported symptom frequency. Error bars represent SD. Data missing for one patient at days 7 and 14 (due to study discontinuation). *$P < 0.0001$ versus baseline (paired t test). *SD* standard deviation

Table 2 Ocular Surface Disease Index scores

	Baseline Mean (SD)	Day 14 Mean (SD)	Change from baseline Mean (SD)
OSDI total score*	50.5 (16.7)	18.4 (13.9)	− 32.1 (18.1) $P < 0.0001$
Ocular symptom subtotal (items 1–5)†	8.9 (3.5)	3.7 (2.8)	− 5.2 (3.8) $P < 0.0001$
Vision-related function subtotal (items 6–9)‡	7.3 (4.1)	2.0 (2.4)	− 5.3 (4.0) $P < 0.0001$
Environmental triggers subtotal (items 10–12)§	6.7 (3.4)	2.6 (2.6)	− 4.0 (3.4) $P < 0.0001$

OSDI Ocular Surface Disease Index, *SD* standard deviation

*Calculated as [(sum of all item scores) × 25] / # of items answered; each item scored from 0–4; possible score range, 0–100

†Each item scored from 0–4; possible score range, 0–20

‡Each item scored from 0–4; possible score range, 0–16

§Each item scored from 0–4; possible score range, 0–12

60 min after instillation on day 1 and continued improvement observed through day 14. Ratings of symptom severity and frequency were reduced by 40% or more at day 3 and 55% or more at day 14. On the OSDI, there was significant improvement in ocular symptoms, vision-related function, and environmental triggers. The frequency of fluctuating vision, a common symptom of evaporative DED that can interfere with daily activities [20], was markedly reduced early in PFHO treatment.

These findings support and extend the evidence from RCTs, which found that reduction in both symptoms and signs of DED was significantly greater for PFHO versus a hypotonic saline control after 2 weeks of treatment [14–16]. PFHO demonstrated excellent tolerability in this study, consistent with the findings of RCTs [14–16, 21] and a 12-month open-label extension study [17]. The safety and efficacy of PFHO were evaluated in two independent systemic reviews [22, 23]. In a meta-analysis of four RCTs [14–16, 21], PFHO provided significantly greater improvement than saline solution control across multiple DED signs and symptoms, measured as change from baseline at week 8, including eye dryness, eye burning/stinging, OSDI score, tCFS, and central corneal fluorescein staining [23]. The occurrence of ocular adverse events was similar in the PFHO and control groups (risk ratio 1.00; 95% CI 0.77, 1.29) [23]. The superiority of PFHO relative to saline control for reducing patient-reported symptoms and tCFS was similarly reported in a systematic review [22] of six RCTs [14–16, 21, 24, 25]; in addition, increased lipid layer thickness was observed with PFHO versus a cationic emulsion control at week 12, while change in TFBUT was similar between groups.

Other FDA-approved topical pharmacologic treatments for DED include 0.05% cyclosporine ophthalmic emulsion (Restasis®; Allergan), 0.09% cyclosporine ophthalmic solution (Cequa®, Sun Pharmaceutical) nonaqueous 0.1% cyclosporine ophthalmic solution (Vevye®, Harrow Eye), lifitegrast ophthalmic solution 5.0% (Xiidra®, Bausch + Lomb), and varenicline solution nasal spray (Tyrvaya®, Oyster Point Pharma) [26]. Cyclosporine [27–29] and lifitegrast [30, 31] have anti-inflammatory properties, and presumably treat DED by reducing ocular surface inflammation. Cyclosporine acts primarily to inhibit activation of T cells, whereas lifitegrast inhibits the migration and recruitment of previously activated T cells as well as the activation of resting T cells [31]. Varenicline is thought to

stimulate tear production via activation of the trigeminal parasympathetic pathway [32].

Limited information is available regarding early outcomes for these DED treatments. In pivotal trials, DED signs and symptoms were assessed at scheduled intervals, with the earliest postbaseline symptom data generally reported for week 2 or week 4 [33–42]. In an open-label survey study of more than 5000 patients treated with 0.05% cyclosporine ophthalmic emulsion, 32% reported onset of symptom relief within 1 week and 73% within 3 weeks [43]. To our knowledge, no DED product other than PFHO has demonstrated symptom relief as early as 5 min after the first instillation, with maintenance of effect after 1 h and continued improvement with consistent use.

A strength of the present study is that each patient identified their most bothersome symptom, which provided an individualized assessment of treatment effectiveness. Study limitations include the open-label design, absence of a control group, lack of assessment of clinical signs of DED (e.g., corneal fluorescein staining, TFBUT, lipid layer thickness, MGD score), and limited diversity of the study population. The magnitude of reduction in eye dryness after 2 weeks of treatment was larger in this study than in the RCTs of PFHO [14–16], as is often observed in open-label studies. As signs and symptoms of DED are often uncorrelated [44], potential effects of PFHO on clinical signs of DED during the first 2 weeks of treatment are unknown. Notably, RCTs of PFHO demonstrated efficacy for treating both the signs and symptoms of DED beginning at week 2 and continuing thereafter [14, 15]. Future RCTs are needed to evaluate the impact of PFHO on meibum-related variables (eg, Meibomian gland yielding secretion score [MGYSS], Meibomian gland yielding clear secretion [MGYCS], Meibomian gland yielding liquid secretion [MGYLS]). The current study population was primarily older (mean age of 61 years), female, and white, and additional research is needed to confirm the early effects of PFHO in other demographic groups. On the other hand, the inclusion of a substantial number of postmenopausal women indicates that PFHO was effective in this group, who are commonly diagnosed with DED.

CONCLUSION

This study found that patients with DED experienced significant and meaningful reductions in the severity and frequency of dry eye symptoms within the first 2 weeks of treatment with PFHO, and satisfaction with treatment was high.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jason Bacharach reports being a consultant and conducting research for Bausch + Lomb. Shane R. Kannarr reports serving as a consultant, being a speaker, or conducting research for Alcon, Allergan, Bausch + Lomb, CooperVision, Essilor, Johnson & Johnson Vision, Novartis, Ocuphire Pharma, RVL Pharmaceuticals, Sight Sciences, Tarsus Pharmaceuticals, Vision Source, and Visus Therapeutics. Anthony Verachtert reports nothing to disclose. Preeya K. Gupta reports serving as a consultant for Alcon, Aldeyra Therapeutics, Inc, Allergan, Azura, Bausch + Lomb, Dompé, Expert Opinion, HanAll Biopharma, Johnson & Johnson Vision, Kala Pharmaceuticals, Mazado, Inc, Nordic Pharma, Ocular Science, Oculis, Orasis, ScienceBased Health, Sight Sciences, SpyGlass Pharma, Surface Ophthalmics, Tarsus Pharmaceuticals, TearClear, Théa Pharma, Tissue Tech, Trukera Medical, Viatris, Visionology, Vital Tears, and Zeiss; and having stock options in Azura, Expert Opinion, Orasis, SpyGlass Pharma, Surface Ophthalmics, Tarsus Pharmaceuticals, TearClear, and Visionology. Moataz Razeen, Megan E. Cavet and Jason L. Vittitow are employees of Bausch + Lomb. Jacob Lang reports serving as a consultant to Alcon, Allergan, Aldeyra Therapeutics, AOS, AscuelaTech, Avellino, Bausch + Lomb, Dompé, Envision Biomedical, Horizon, Kala Pharmaceuticals, Novartis, Orasis, Oyster Point Pharma, Science Based Health, Scope, Sight Sciences, Sun Pharmaceutical Industries, Tarsus, Théa Pharma, Trukera Medical, and Zeiss; and as a speaker for Dompé, Oyster Point Pharma, and Sun Pharmaceutical Industries. Thomas M. Chester reports serving as a consultant/speaker for Bausch + Lomb, Sight Sciences, Tarsus, and Viatris. Jillian F. Ziemanski reports receiving research support from Bausch + Lomb. Darrell E. White reports serving as a consultant and speaker to Bausch + Lomb.

Ethical Approval. The study was approved by the Advarra Institutional Review Board (IRB Registration number 00000971). This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, and all patients provided informed consent to participate in the study.

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