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Long-Term Safety and Efficacy of Perfluorohexyloctane Ophthalmic Solution for the Treatment of Patients With Dry Eye Disease: The KALAHARI Study

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Purpose: The aim of this study was to assess the long-term safety and efficacy of perfluorohexyloctane (PFHO) ophthalmic drop (formerly NOV03) for treatment of dry eye disease (DED).

Methods: KALAHARI was a phase 3, multicenter, single-arm, open-label extension study in patients aged 18 years or older with DED associated with Meibomian gland dysfunction who completed the randomized, double-masked, hypotonic saline-controlled GOBI study. Patients instilled 1 drop of PFHO (MIEBO, Bausch + Lomb) 4 times daily in both eyes for 52 weeks. Safety assessments included adverse events, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, and dilated fundoscopy. Efficacy end points included change from GOBI study baseline in total corneal fluorescein staining and eye dryness score (0–100 visual analog scale).

Results: Overall, 208 patients from GOBI (PFHO [n = 97]; saline [n = 111]) were rolled over into KALAHARI. Twenty-nine patients (13.9%) had ≥1 ocular adverse event, with most being mild or moderate in severity; the most common ocular adverse events were vitreous detachment (1.9%), allergic conjunctivitis (1.4%), blurred vision (1.4%), and increased lacrimation (1.4%). Other safety end points were unremarkable. For patients continuing PFHO from GOBI, improvements in total corneal fluorescein staining and visual analog scale dryness scores observed in GOBI were maintained throughout KALAHARI. Patients treated with saline in GOBI and switched to PFHO in KALAHARI showed improvements in total corneal fluorescein staining and visual analog scale scores by week 4 that were maintained for the rest of the study.

Conclusions: PFHO was safe and well tolerated and maintained efficacy for improving signs and symptoms of DED in this year-long study of patients with DED associated with Meibomian gland dysfunction.

Key Words: clinical trial, dry eye disease, Meibomian gland dysfunction, NOV03, perfluorohexyloctane

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Dry eye disease (DED) is a common, chronic disorder affecting the ocular surface.[1] DED is characterized by ocular symptoms (eg, dryness, irritation, or stinging) and signs that include reduced tear fluid, tear film instability, and ocular surface damage.[2,3] DED negatively affects patients' quality of life, daily activities, and work productivity and performance because of the chronic nature of DED symptoms.[3,4] DED can be subclassified as aqueous-deficient, in which lacrimal secretion is decreased, or evaporative, in which tear film evaporation is excessive.[1,5] Most patients present with evaporative DED, which is primarily caused by Meibomian gland dysfunction (MGD), and many patients have a mixed subtype that includes both aqueous-deficient and evaporative components.[6]

Meibomian glands produce lipid-rich secretion (meibum) that is spread onto the tear film by blinking.[5] Meibum is the primary source of lipids in the tear film lipid layer, which protects the aqueous component of the tear film from evaporation.[7] In patients with DED associated with MGD, the tear film lipid layer is altered, which leads to increased tear evaporation and tear film instability.[5] This results in tear hyperosmolarity and desiccation, leading to increased inflammation and apoptosis, and a chronic cycle of DED.[8]

Initial management of DED associated with MGD typically includes home-based therapies (eg, warm compresses, lid hygiene, and over-the-counter artificial tears).[9,10] However, adherence to home-based regimens is often poor,[11] and most patients with DED are not satisfied with dry eye symptom relief from over-the-counter products.[4] The next step in treatment often involves office-based therapies (eg, thermal pulsation or intense light therapy) and/or prescription

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The data sets generated during and/or analyzed during the current study are not available.

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medications.[10] Ophthalmic formulations approved by the US Food and Drug Administration (FDA) for the treatment of DED include cyclosporine, lifitegrast, and loteprednol etabonate 0.25%.[12–14] Varenicline solution nasal spray, a cholinergic agonist intended to increase tear production, is also FDA-approved.[15,16] However, none of these prescription medications is focused on addressing the leading driver of DED, namely, evaporation.[10]

Perfluorohexyloctane (PFHO; MIEBO, Bausch + Lomb, Bridgewater, NJ; previously known as NOV03) is a novel, nonaqueous, preservative-free ophthalmic drop consisting of 100% PFHO that was recently approved by the FDA for the treatment of signs and symptoms of DED.[17] In the phase 2, randomized, double-masked, saline (0.9%)-controlled SEECASE clinical study, PFHO (administered 2 or 4 times daily) improved total corneal fluorescein staining (tCFS) and visual analog scale (VAS) dryness scores from baseline after 8 weeks of treatment in adults with DED associated with MGD.[18] Furthermore, PFHO (administered 4 times daily) significantly improved tCFS and VAS dryness scores in the phase 3, randomized, double-masked, hypotonic saline (0.6%)-controlled GOBI and MOJAVE clinical studies, with onset of efficacy observed as early as week 2 and sustained through the 8-week treatment period.[19,20] The efficacy of PFHO in improving both signs and symptoms of DED was also demonstrated in a randomized, double-masked, saline-controlled study in Chinese patients with DED associated with MGD.[21] PFHO had a favorable safety profile and was well tolerated by patients in all these clinical studies.[18–21] Although PFHO has demonstrated efficacy and safety in these 8-week studies,[18–21] DED is a chronic disease, and patients require long-term management. The objective of this open-label extension study (KALAHARI) was to evaluate the long-term safety and efficacy of PFHO in a subset of patients who continued to use PFHO or switched from hypotonic saline to PFHO after completing the phase 3 GOBI study.

MATERIALS AND METHODS

Study Design

KALAHARI, a 52-week, phase 3, multicenter, single-arm, open-label extension of the GOBI study, was conducted at 22 investigational sites in the United States between September 2020 and January 2022. The open-label design was based on guidance and approval from the FDA. Eligible patients were adults (aged 18 years or older) with a self-reported history of DED in both eyes for ≥6 months and clinical signs of MGD who had also participated in the randomized, double-masked, hypotonic saline-controlled GOBI study and were enrolled at GOBI study investigational sites that had agreed a priori to also participate in KALAHARI. To be eligible for inclusion KALAHARI, patients had to have completed the GOBI study with no major protocol deviations. Details regarding the GOBI study have been published.[19]

Patients were instructed to instill 1 drop of PFHO 4 times daily in both eyes for 52 weeks. Study visits were scheduled at 6 time points during KALAHARI: day 1 (the last GOBI study visit) and weeks 4, 12, 26, 40, and 52. After week 4, the adjunctive use of artificial tears (preferably preservative-free) was allowed; other treatments for DED (eg, gels, ointments, or intranasal tear neurostimulator) could be used after an unsuccessful trial of artificial tears. Physical ocular therapies (eg, lid scrubs or lid wipes) were permitted. Topical prescription medications were allowed, if necessary, per the investigator's judgment. Treatment compliance was evaluated using patient dosing diaries and calculated as the total number of doses administered, divided by the total number of doses that should have been administered, multiplied by 100.

This study was conducted in accordance with the Good Clinical Practice guideline of the International Conference on Harmonization and the tenets of the Declaration of Helsinki. The study protocol was approved by institutional review boards associated with the individual study sites. All patients provided written informed consent before initiation of any study-related procedures. The study was registered at ClinicalTrials.gov (identifier NCT04140227).

Outcome Measures

The primary safety end point was the occurrence of ocular and nonocular adverse events (AEs). Secondary safety end points were best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP), and dilated fundoscopy. Slit-lamp biomicroscopy (including an external eye examination) was used to evaluate the status of the lids, cornea, conjunctiva, anterior chamber, iris, and lens; dilated fundoscopy included assessment of the vitreous, retina, macula, choroid, and optic nerve. IOP was measured using contact tonometry. Investigators rated the slit-lamp biomicroscopy and dilated fundoscopy findings as normal or abnormal.

Efficacy assessments included investigator-rated corneal fluorescein staining and patient-reported symptom severity (eg, eye dryness or burning/stinging) and Ocular Surface Disease Index (OSDI), which were assessed at each postbaseline visit in the KALAHARI study (day 1 and weeks 4, 12, 26, 40, and 52). Fluorescein staining of 5 areas of the cornea (inferior, superior, central, nasal, and temporal) was rated by the investigator according to the National Eye Institute (NEI) scale (grade 0 [no staining] to grade 3 [heavy staining]); the tCFS score was the sum of the individual scores (maximum, 15). Patients rated eye dryness and other symptoms for both eyes using a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort). The patient-rated OSDI uses a scale from 0 to 100, with higher scores indicative of greater symptom severity. In addition, a questionnaire was administered (day 1 and week 52) to assess patient comfort and acceptability of PFHO using a VAS ranging from 0 to 10, with higher scores representing greater comfort and ease of use.

Efficacy end points included change from GOBI study baseline in tCFS, subregion corneal fluorescein staining (CFS), VAS eye dryness score, other ocular symptom VAS scores (ie, burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, awareness of dry eye symptoms, and frequency of dryness), and OSDI score. The proportion of responders was calculated for tCFS (defined as an improvement of ≥3 steps from GOBI baseline on the NEI scale)

and eye dryness (defined as ≥30% reduction from GOBI baseline in the VAS score).

Statistical Analysis

The initial sample size planned for the inclusion of approximately 200 patients to ensure that ≥100 evaluable patients completed the week 26 and week 52 treatment periods, which would provide a ≥95% chance of observing AEs that occurred at a true incident rate of ≥3%. To account for any potential negative effects on enrollment due to COVID-19, the sample size was later increased to include approximately 250 patients. The safety population included all patients who received ≥1 dose of study drug. Analyses of prespecified efficacy end points were conducted using the safety population with all available data per patient; no formal statistical analyses were conducted, and change from baseline was defined as a change from GOBI study baseline. Safety and efficacy results were summarized by treatment group (according to GOBI assignments for the safety population) and overall (both groups combined).

RESULTS

Patients

The safety population included 208 patients from the GOBI study (97 patients continued to use PFHO and 111 patients switched from saline to PFHO) who continued into the open-label KALAHARI extension study (Fig. 1). Overall, 160 patients (76.9%) completed and 48 (23.1%) discontinued the study. One patient died because of an AE of gastric cancer, which was considered unrelated to study medication.

Overall, patients in the KALAHARI study had a mean age of 61.2 years; most (70.2%) were female patients and 63.9% were White (Table 1). For patients included in the KALAHARI study, at GOBI study baseline, the mean tCFS in the study eye was 6.6 and the mean VAS dryness score was 67.7. Baseline ocular characteristics were similar between patients who were assigned to PFHO or saline in the GOBI study. Most patients (93.8%) were considered compliant with PFHO dosing (defined as administration of 80%–120% of the expected doses), and compliance was comparable between patients in the PFHO continuation group (94.8%) and the saline switch group (92.8%). Overall, 14 patients (6.7%) took ≥1 concomitant ocular medication (in either eye) during the KALAHARI study. Ten patients (4.8%) used adjunctive artificial tears/mineral oil, as permitted after week 4. Other concomitant ocular medications used by ≥1 patient were ofloxacin (n = 2 [1.0%]), dexamethasone/neomycin sulfate/polymyxin B sulfate (n = 2 [1.0%]), and dexamethasone/tobramycin (n = 2 [1.0%]).

Major protocol violations were reported in 45 patients (21.6%) overall, including 14 (14.4%) in the PFHO continuation group and 31 (27.9%) in the saline switch group. The most common major protocol violations were study visit/schedule deviations (ie, >2 days before or after week 4 visit or >7 days before or after week 12, 26, 40, and 52 visits; 21 events overall: PFHO continuation group [n = 4] vs. saline switch group [n = 17]) and investigational product deviation/compliance (<80% compliant in dosing, drops not administered as per protocol; 14 events overall: PFHO continuation group [n = 5] vs. saline switch group [n = 9]).

Safety

Ocular AEs

Ocular AEs were experienced by 13.9% of patients overall, with 6.3% of patients reporting ≥1 ocular treatment-related AE (Table 2). AE profiles were comparable between

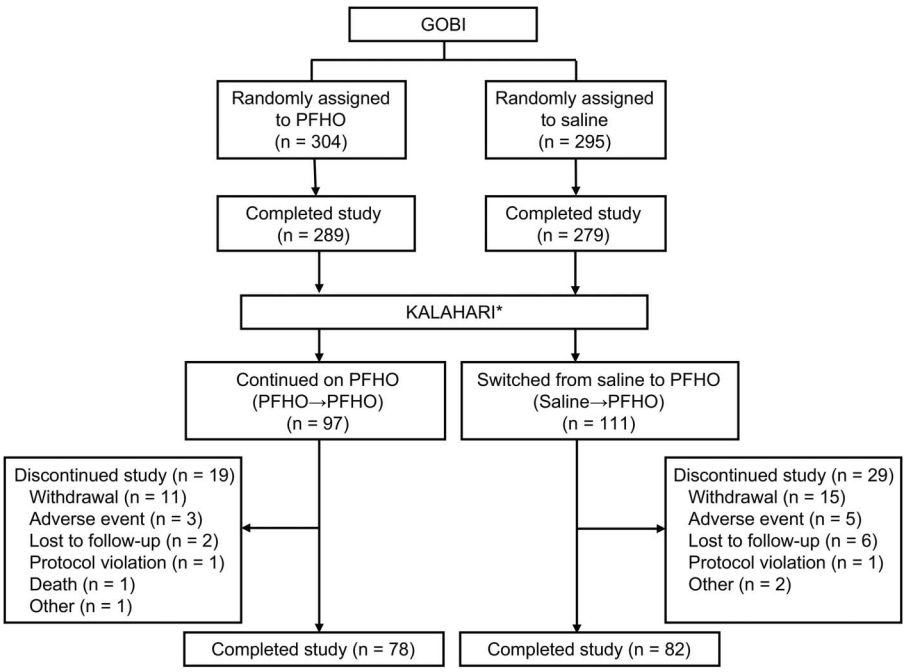

FIGURE 1. Patient disposition. *A subset of patients who completed GOBI enrolled in KALAHARI. PFHO→PFHO, PFHO continuation group; saline→PFHO, saline switch group

TABLE 1. Demographic and Baseline Clinical Characteristics

Characteristic	All Patients (n = 208)	PFHO→PFHO (n = 97)	Saline→PFHO (n = 111)
Age, mean (min, max), y	61.2 (19–88)	61.2 (19–87)	61.3 (24–88)
≥65 y, n (%)	94 (45.2)	39 (40.2)	55 (49.5)
Female, n (%)	146 (70.2)	65 (67.0)	81 (73.0)
Race, n (%)			
Asian	29 (13.9)	13 (13.4)	16 (14.4)
Black	43 (20.7)	23 (23.7)	20 (18.0)
White	133 (63.9)	61 (62.9)	72 (64.9)
Other/unknown	3 (1.4)	0	3 (2.7)
GOBI study baseline ocular characteristics, mean (SD)			
tCFS score, study eye	6.6 (1.7)	6.5 (1.7)	6.6 (1.8)
VAS dryness score	67.7 (19.8)	66.9 (20.6)	68.4 (19.1)
VAS burning/stinging score	53.0 (28.2)	49.0 (29.2)	56.5 (27.0)
Total MGD score*	7.1 (3.1)	6.9 (3.2)	7.3 (3.0)
TFBUT, study eye, s	3.2 (0.8)	3.1 (0.7)	3.3 (0.9)
Unanesthetized Schirmer I test, study eye, mm	12.0 (8.1)	11.7 (8.2)	12.2 (8.0)
OSDI score	55.0 (17.8)	54.2 (17.8)	55.7 (18.0)
BCVA (logMAR)	0.09 (0.1)	0.09 (0.1)	0.09 (0.1)
IOP, mm Hg	15.3 (2.7)	15.3 (2.8)	15.2 (2.6)

logMAR, logarithm of the minimum angle of resolution; PFHO→PFHO, PFHO continuation group; Saline→PFHO, saline switch group; TFBUT, tear film break-up time.
*Based on evaluation of secretions from the 5 central Meibomian glands of the lower eyelid. Investigators scored each gland secretion from 0 to 3: 0 = normal; 1 = thick/yellow, whitish, particulate; 2 = paste; and 3 = none/occluded. Thus, the total MGD score ranged from 0 to 15.

the PFHO continuation group and saline switch group. Rates of specific ocular AEs were low; the most common ocular AEs were vitreous detachment (1.9% of patients, none considered treatment-related), allergic conjunctivitis (1.4%), blurred vision (1.4%), and increased lacrimation (1.4%). Most ocular AEs were mild or moderate in severity. One patient experienced a severe ocular AE (eyelid irritation in both eyes, which the investigator considered possibly related to study medication); however, this AE did not result in treatment discontinuation. No serious ocular AEs occurred. Ocular AEs leading to discontinuation of study medication were reported in 5 patients (2.4%) (1 patient each with blurred vision, chalazion, dry eye, increased lacrimation, and increased IOP). Three of these AEs were considered treatment-related (blurred vision, chalazion, and increased lacrimation), and all but 1 (chalazion) were reported resolved.

TABLE 2. Summary of Ocular AEs During the KALAHARI Study

Parameter, n (%)	All Patients (n = 208)	PFHO→PFHO (n = 97)	Saline→PFHO (n = 111)
Patients with ≥1 ocular AE*	29 (13.9)	16 (16.5)	13 (11.7)
Mild	21 (10.1)	9 (9.3)	12 (10.8)
Moderate	7 (3.4)	6 (6.2)	1 (0.9)
Severe	1 (0.5)	1 (1.0)	0 (0)
Treatment-related ocular AEs†	13 (6.3)	7 (7.2)	6 (5.4)
Serious ocular AEs	0 (0)	0 (0)	0 (0)
Ocular AEs leading to discontinuation	5 (2.4)	3 (3.1)	2 (1.8)
Most common ocular AEs*,‡			
Vitreous detachment	4 (1.9)	2 (2.1)	2 (1.8)
Allergic conjunctivitis	3 (1.4)	2 (2.1)	1 (0.9)
Blurred vision	3 (1.4)	0 (0)	3 (2.7)
Increased lacrimation	3 (1.4)	3 (3.1)	0 (0)
Chalazion	2 (1.0)	1 (1.0)	1 (0.9)
Dry eye	2 (1.0)	2 (2.1)	0 (0)
Hordeolum	2 (1.0)	1 (1.0)	1 (0.9)
Instillation site pain	2 (1.0)	1 (1.0)	1 (0.9)

PFHO→PFHO, PFHO continuation group; Saline→PFHO, saline switch group.
*Patients instilled drops in both eyes; values represent n (%) of patients with an AE in either eye.
†Considered by the investigator as suspected to be or related to study medication.
‡Incidence ≥2 patients in overall population.

Nonocular AEs

Overall, 51 patients (24.5%) had ≥1 nonocular AE, with most patients experiencing AEs that were mild (n = 26 [12.5%]) or moderate (n = 21 [10.1%]) in severity. Nonocular serious AEs, none of which were considered treatment-related, were reported in 10 patients (4.8%) (PFHO continuation group, n = 4 [4.1%]; saline switch group, n = 6 [5.4%]). One death occurred (gastric cancer), which was not considered related to study medication. Four patients (1.9%) had a nonocular AE leading to treatment discontinuation (bladder cancer, cerebrovascular accident, schizophrenia, and subdural hematoma); none of these AEs were considered treatment-related.

Other Safety Outcomes

There were few clinically meaningful findings in BCVA, IOP, slit-lamp biomicroscopy, or dilated fundoscopy assessments, and none were indicative of a safety concern with the long-term use of PFHO. Mean BCVA fluctuated slightly throughout the study but remained essentially unchanged from GOBI baseline (mean [SD] change at week 52, –0.01 [0.09] logMAR). Changes from baseline in IOP were minimal throughout the study. Study eye IOP at week 52 was also essentially unchanged from GOBI study baseline (mean [SD] change, −0.1 mm Hg [2.8]). Baseline slit-lamp biomicroscopy and dilated fundoscopy examinations were consistent with patient age and the disease under investigation, and less than 1.4% of patients showed worsening in a slit-lamp examination result or a dilated fundoscopy result in the study eye at any given postbaseline visit. Overall, patients were satisfied with PFHO treatment (mean VAS score [SD] at week 52, 8.0 [2.3]) and found the study eye drops to be comfortable (8.4 [2.1]) and easy to administer (8.9 [1.9]).

Efficacy

Throughout the study, mean tCFS and VAS dryness scores (GOBI primary end points) were improved relative to GOBI baseline. For tCFS score, mean (SD) change from GOBI baseline in the study eye was −1.8 (2.3) at week 4, –1.8 (2.4) at week 12, –2.2 (2.3) at week 26, –2.2 (2.3) at week 40, and –2.1 (2.5) at week 52. Similar findings were observed in the fellow eye. For VAS dryness score (both eyes), mean (SD) change from GOBI baseline was −26.5 (26.5) at week 4, –27.5 (26.5) at week 12, –30.0 (26.6) at week 26, –29.9 (27.5) at week 40, and –33.7 (28.6) at week 52.

For patients in the PFHO continuation group, improvements in tCFS (study eye) and VAS dryness scores observed in GOBI were maintained during KALAHARI (Figs. 2A, B). Patients in the saline switch group had improvements in tCFS (study eye) and VAS dryness scores by week 4 of KALAHARI that were maintained through week 52.

For CFS score in the central subregion (a GOBI study key secondary end point), mean (SD) change from GOBI baseline with PFHO in the overall patient population was −0.3 (0.9) at week 4, –0.2 (0.9) at week 12, –0.3 (0.8) at week 26, –0.4 (0.8) at week 40, and –0.3 (0.9) at week 52 in the study eye; similar findings were observed in the fellow eye. For CFS score in the inferior subregion (study eye), mean (SD) change from baseline was −0.4 (0.8) at week 4, –0.3 (0.9) at week 12, –0.5 (0.9) at week 26, –0.4 (0.9) at week 40, and –0.5 (0.9) at week 52; findings were similar in the fellow eye.

Throughout the study, mean ocular symptom scores were improved relative to GOBI baseline (Table 3). For VAS burning/stinging score (a GOBI study key secondary end point), mean (SD) change from baseline was −24.0 (28.4) at week 4, –23.6 (26.6) at week 12, –26.1 (27.8) at week 26, –24.7 (29.8) at week 40, and –30.0 (27.9) at week 52. For the OSDI total score, mean (SD) change from baseline was −23.1 (18.2) at week 4, –25.0 (19.1) at week 12, –24.9 (18.9) at week 26, –25.6 (18.9) at week 40, and –27.1 (18.8) at week 52. Mean decreases from baseline in VAS scores and OSDI scores were generally similar between the PFHO continuation group and the saline switch group by week 4 and were maintained for the rest of the study.

The percentage of patients who met the criteria defining tCFS responders and VAS dryness responders was consistent throughout the study (Fig. 3). Response rates were comparable between patients in the PFHO continuation and saline switch groups.

DISCUSSION

KALAHARI examined the long-term safety and efficacy of PFHO in patients with DED associated with MGD. Short-term efficacy and safety were consistently demonstrated in the 8-week phase 2 SEECASE, phase 3 GOBI, and phase 3 MOJAVE studies, as well as a phase 3 study conducted in China, in patients with DED associated with MGD.[18–21] In KALAHARI, patients were administered PFHO for 52 weeks; thus, patients who were randomized to PFHO in GOBI were exposed to a cumulative 60 weeks of PFHO treatment during the combined GOBI and KALAHARI study periods. Long-term use of PFHO 4 times daily was safe and well tolerated in patients in the KALAHARI study, with a safety profile consistent with that reported in previous short-term studies of PFHO.[18–21] During the year-long treatment period, no single ocular AE occurred at an incidence ≥2.0%, and ocular AEs were considered treatment-related in fewer than half of the patients. There was a low rate of instillation site reaction in this study (1.0%), which confirms the favorable tolerability previously reported.[18–21] PFHO has been designed to be well tolerated; it is a single-ingredient product that requires no preservatives and has a small drop size—all important characteristics for the chronic treatment of patients with DED. Furthermore, because PFHO is a nonaqueous drop, it does not have a pH; therefore, instillation of PFHO is not expected to cause a burning sensation, as has been observed for topical ocular products with a pH outside the physiological range. Results of additional safety outcomes (ie, BCVA, IOP, slit-lamp biomicroscopy, and dilated fundoscopy) indicated that long-term use of PFHO was not associated with safety concerns in patients with DED associated with MGD. As expected, the safety profiles were comparable for patients who continued to use PFHO versus

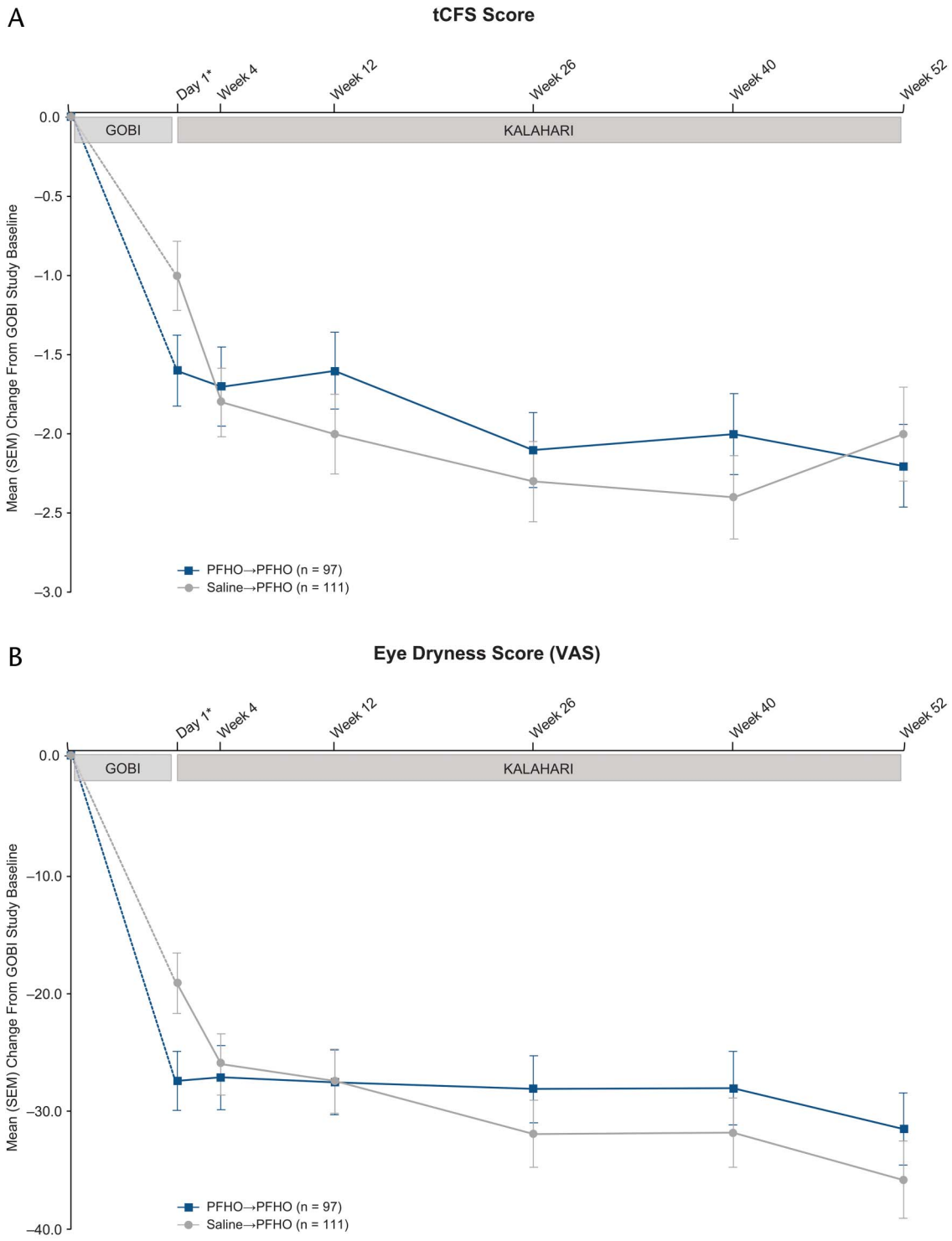

FIGURE 2. Mean change from GOBI study baseline in (A) tCFS score (study eye) and (B) eye dryness score (VAS) by study visit: GOBI–KALAHARI. *KALAHARI day 1 is the final visit in the GOBI study. Dashed lines represent GOBI treatment (PFHO, saline). tCFS score range: grade 0 (no staining) to grade 3 (heavy staining) for 5 areas of the cornea (maximum score, 15). VAS score range (both eyes simultaneously): 0 (no discomfort) to 100 (maximal discomfort). PFHO→PFHO, PFHO continuation group; Saline→PFHO, saline switch group; SEM, standard error of mean. (The full color version of this figure is available at www.corneajrnl.com.)

TABLE 3. Change From GOBI Baseline in Ocular Symptom VAS Scores

VAS Score	GOBI Baseline, Mean (SD)	Mean (SD) Change From GOBI Baseline at the KALAHARI Study Visits					
		Day 1*	Week 4	Week 12	Week 26	Week 40	Week 52
Dryness	67.7 (19.8)	−23.0 (26.3)	−26.5 (26.5)	−27.5 (26.5)	−30.0 (26.6)	−29.9 (27.5)	−33.7 (28.6)
Burning/stinging	53.0 (28.2)	−19.3 (26.1)	−24.0 (28.4)	−23.6 (26.6)	−26.1 (27.8)	−24.7 (29.8)	−30.0 (27.9)
Sticky feeling	47.8 (26.3)	−12.1 (28.3)	−14.6 (31.7)	−15.7 (30.0)	−16.5 (28.3)	−16.8 (27.7)	−22.9 (28.9)
Foreign body sensation	50.4 (29.4)	−15.2 (29.9)	−17.9 (30.3)	−20.6 (29.3)	−22.4 (30.0)	−24.0 (28.0)	−24.2 (29.0)
Itching	55.1 (28.4)	−18.8 (26.4)	−22.9 (28.2)	−23.6 (26.7)	−27.1 (28.6)	−25.7 (30.3)	−28.3 (30.2)
Blurred vision	56.2 (27.4)	−16.4 (28.2)	−19.5 (28.0)	−22.1 (28.3)	−21.6 (27.8)	−19.8 (29.0)	−23.8 (30.1)
Sensitivity to light	57.1 (27.5)	−16.5 (28.0)	−18.1 (28.6)	−19.2 (29.4)	−25.3 (28.1)	−22.4 (29.7)	−26.8 (30.1)
Pain	37.1 (27.5)	−13.7 (26.9)	−18.3 (26.8)	−19.6 (25.6)	−20.3 (25.9)	−19.8 (26.9)	−23.8 (26.3)
Awareness of dry eye symptoms	72.0 (22.3)	−21.4 (29.5)	−25.4 (29.9)	−25.7 (29.2)	−27.2 (29.3)	−27.9 (28.5)	−31.1 (30.7)
Frequency of dryness	72.8 (21.7)	−24.2 (28.7)	−26.4 (27.7)	−27.0 (28.7)	−28.3 (28.2)	−31.3 (26.4)	−33.4 (30.6)

*Day 1 visit is equivalent to the week 8 (final) visit in the GOBI study.

patients who switched from saline to PFHO in this study, further validating the favorable safety and tolerability of PFHO. As well, overall, patients reported that the PFHO drops were comfortable and easy to use.

Improvements in tCFS and VAS dryness scores observed at the end of GOBI were maintained for the duration of KALAHARI in patients who received PFHO in both studies (ie, PFHO continuation group). As was observed after initiation of treatment with PFHO in short-term studies, the onset of effect was rapid for patients who switched from saline in the GOBI study to PFHO in KALAHARI (ie, saline switch group), and these benefits were sustained for the duration of the study. Improvements in tCFS, VAS eye dryness score, VAS burning/stinging score, and central CFS indicate maintenance of corneal healing through 52 weeks, regardless of the patients' treatment assignment in GOBI. Inconsistencies in the evaluation of signs and symptoms of DED in clinical studies have proven to be a challenge for other DED treatments,[2] and there are a limited number of published studies on efficacy with chronic use.[22–24] The long-term efficacy for both signs and symptoms within 1 population, observed in this study of PFHO, build on the consistent efficacy results observed in the SEECASE,[18] GOBI,[19] and MOJAVE[20] short-term studies, indicating that PFHO may be a safe and efficacious long-term treatment option for patients with DED. Ratings of patient satisfaction (based on VAS scores for instillation comfort and drop acceptability) were high, and only a small number of patients (4.8%) reported concomitant use of artificial tears/mineral oil, further indicating that PFHO provided relief from the symptoms of DED over a year-long period.

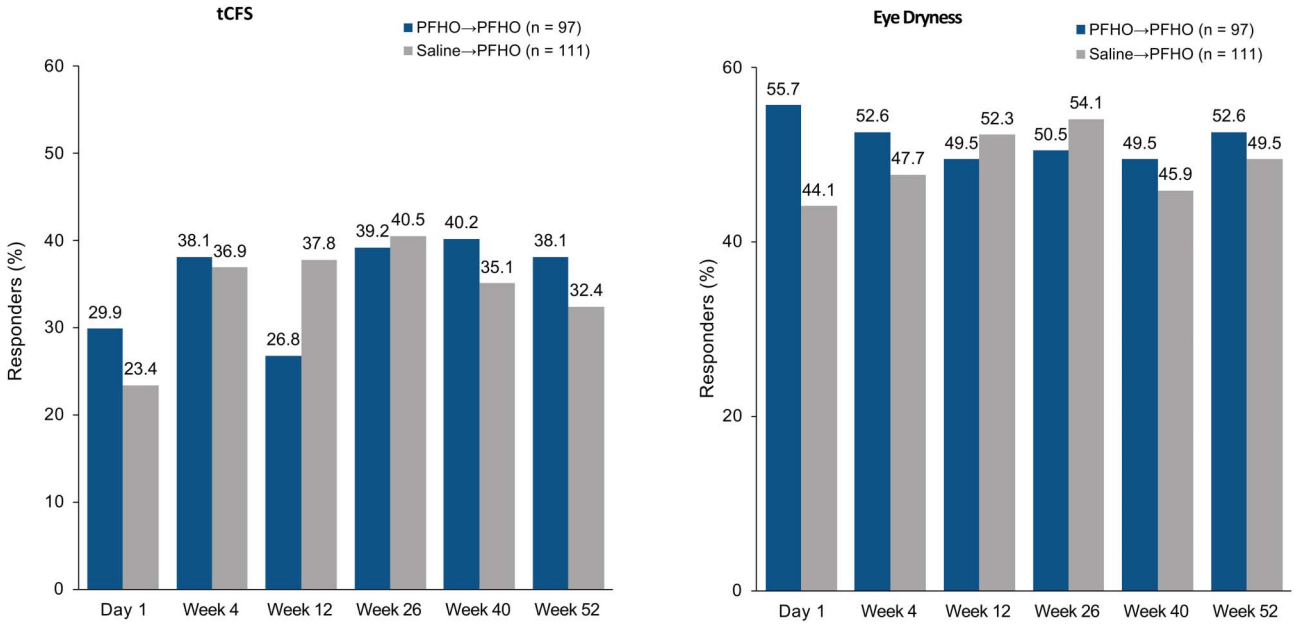

FIGURE 3. Response rates for tCFS* (study eye) and eye dryness† in KALAHARI. *Response defined as ≥3-step improvement (NEI scale) from GOBI baseline. †Response defined as ≥30% improvement (VAS score) from GOBI baseline. ‡KALAHARI day 1 is the final visit in the GOBI study. (The full color version of this figure is available at www.corneajrnl.com.)

PFHO spreads rapidly over the ocular surface because of its low surface tension and forms a monolayer at the air–liquid interface, which, in turn, creates a barrier to evaporation of the aqueous layer of the tear film and thereby diminishes the signs and symptoms of DED.[25–27] Excessive evaporation is a primary underlying etiology of DED,[10] and PFHO is the first and only prescription eye drop that has been shown to inhibit evaporation.[27] Residence time of PFHO in the tears, as observed in a preclinical rabbit study, was at least 6 hours.[28] PFHO is believed to serve as a potential replacement or supplement for the dysfunctional tear film lipid layer in patients with DED associated with MGD.[27] However, the resulting reduced evaporation of the aqueous layer of the tear film is expected to benefit both patients with DED associated with MGD and DED due to aqueous deficiency. Results of the KALAHARI study indicate that PFHO safely and effectively improves signs and symptoms of DED over the long term, which is important given the chronic nature of DED.[1] No waning of efficacy was observed in the PFHO continuation group vis-à-vis the GOBI study, attesting to the efficacy of PFHO through as long as 60 weeks of usage.

Study limitations include the open-label design, lack of a control group, and exclusion of patients with severe dry eye (tCFS score >11). Although the subset of patients who enrolled in KALAHARI were de facto motivated to stay longer in the study, and potentially more likely to report improvement, patient-reported VAS dryness scores in KALAHARI were highly consistent not only with VAS dryness results for PFHO treatment in GOBI[19] but also with those in MOJAVE[20] and SEECASE[18] studies. PFHO administered 4 times daily was safe and well tolerated, and the efficacy for improving signs and symptoms of DED was maintained in this long-term (>1 year) study of patients with DED associated with MGD.

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