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Investigating the Effect of Reducing the Signs and Symptoms of Lid Wiper Epitheliopathy in Patients With Dry Eye Disease With Perfluorohexyloctane

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ABSTRACT

Background: Perfluorohexyloctane (PFHO) acts to prevent the evaporation of the tear film. It has the potential to limit friction related issues between the eye lid margin and the ocular surface. Prior to the present work, this had not yet been evaluated.
Objective: To examine the potential of using perfluorohexyloctane for reducing the signs and symptoms of lid wiper epitheliopathy (LWE).
Methods: Data were collected at 4 visits spanning 2 months. Patients who had symptomatic dry eye and a LWE score of ≥1.0 on the Korb LWE scale were recruited. Participants were randomized to PFHO 4 times a day or no treatment. Lid wiper epitheliopathy was graded at each visit with the Korb and photographic LWE (PLWE) scales. Symptoms were assessed using the Standard Patient Evaluation of Eye Dryness questionnaire and visual analog scales (0–100).
Results: A total of 52 participants were enrolled (mean ± SD age, 49.7 ± 15.7 years; 79% female). Right eyes in the treatment group were significantly more likely to show an improvement of ≥0.5-units in PLWE scores at 2 months than the no treatment group ($P = 0.04$), but no left eye differences were noted. Korb and PLWE scores were significantly better in the treatment group compared with the no treatment group starting at 2 weeks and remained so for the duration of the study (all $P < 0.001$). Standard Patient Evaluation of Eye Dryness scores and dry eye symptoms were significantly better in the treatment than in the no treatment group at the 2-month visit (all $P \leq 0.01$).
Conclusions: Perfluorohexyloctane significantly reduced LWE and improved dry eye symptoms compared with no treatment, suggesting that PFHO may enhance ocular lubrication and reduce friction-related damage. Masked, randomized, trials are still needed to compare PFHO to other treatments in participants with LWE to support generalizability of results. ClinicalTrials.gov study NCT06671041.

Introduction

Lid wiper epitheliopathy (LWE) shows a strong association with dry eye disease (DED) with LWE being reported in about 90% of patients with DED.[1–3] Lid wiper epitheliopathy is stated as a friction-related condition that affects the palpebral conjunctiva that is in

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contact with the globe.[4] In the upper eyelid, this region is located posterior to the mucocutaneous junction, or line of Marx, but before the tarsal fold.[4] The lid wiper region is present on both the upper and lower eyelids; yet, the latter is of less concern with regards to LWE because the lower eyelid moves less with each blink compared with the upper eyelid.[4] If the patient possesses a dysfunctional tear film, such as those with DED, the increased friction with each blink damages the superficial layers of the nonkeratinized stratified squamous epithelium of the palpebral conjunctiva,[4] which with repeated damage presents itself clinically as LWE.[2,5]

A potential reliever of LWE signs and symptoms is perfluorohexyloctane (PFHO*). Perfluorohexyloctane is a preservative-free ophthalmic solution uniquely developed to directly target tear evaporation.[5] Perfluorohexyloctane is the first semifluorinated alkane approved treatment for DED signs and symptoms in the United States.[6] One of the more common signs of DED is meibomian gland dysfunction, which leads to faulty meibum secretion and thus an incomplete lipid layer. Without the lipid layer, tear film evaporation is exacerbated leading to symptoms such as dryness, grittiness, and overall discomfort. Of the currently US Food and Drug Administration–approved pharmacologic options, such as lifitegrast and cyclosporine, which both target inflammation, PFHO is the only drug targeted for preventing tear evaporation.[6–10] The authors hypothesize that PFHO will act to preserve the aqueous layer, which will subsequently aid not only in treating signs and symptoms of DED but also those related to LWE. Therefore, the purpose of this study was to determine if PFHO in participants with DED would be able to reduce ocular surface frictions and subsequently result in a clinically significant improvement of LWE.

Materials and Methods

Participants

This 2-month, 4-visit study was conducted at multiple sites with equal enrollment across sites: Southern College of Optometry (Memphis, Tennessee), West Bay Eye Associates (Warwick, Rhode Island), Maitland Vision Center (Maitland, Florida), and Complete Eye Care of Medina (Minneapolis, Minnesota). The study was approved by the Institutional Review Board (IRB) of Southern College of Optometry (IRB00006733, Study #2023-03-01AS) and conformed to the tenets of the Declaration of Helsinki. Participants were recruited via clinic records, email, and fliers. Participants were screened before the study visit with an IRB-approved phone screening survey. Participants ≥18 years of age who had best corrected visual acuity of 20/100 or better in both eyes and who had symptomatic DED were recruited (Standard Patient Evaluation of Eye Dryness [SPEED] ≥6).[10,11] The SPEED was selected because it focuses on the frequency and severity of the most common DED symptoms (dryness, grittiness, or scratchiness; soreness or irritation; burning or watering, eye fatigue).[12] Participants were also required to have a LWE score of ≥1.0 (measured with Korb grading scale).[1] Participants were excluded if they had a known systemic health condition that altered tear film physiology (eg, primary and secondary Sjögren syndrome), had a history of ocular surgery within the past 12 months, had physical meibomian gland treatment (eg, iLux†) 1 month before enrollment, had a history of severe ocular trauma, active ocular infection or inflammation, were using Accutane or other ocular medications for the duration of the study, or were pregnant or breast feeding. Participants with a condition or in a situation, which in the investigators' opinion, would have put the participant at significant risk, confounded the study results, or significantly interfered with their participation in the study were excluded. For the duration of the study, participants were required to discontinue contact lens wear. Artificial tear use was discontinued at least 1 week before each participant's enrollment and for the duration of the study.

Study design

This study consisted of 4 visits scheduled at similar times of the day: screening/baseline, 2 weeks, 1 month, and 2 months. Demographic information (date of birth, sex, ethnicity, and race) and medical and ocular history were taken at the screening/baseline visit. The SPEED questionnaire was used to determine study eligibility at the screening visit (SPEED ≥6).[10,11] A visual analog scale (VAS, 0–100) was used to determine DED symptoms severity (eye dryness, eye scratchiness, eye gritty/sandy feeling, eye irritation/soreness, eye burning, eye stinging, eye watering, eye fatigue, eye itching, and current eye discomfort). The VAS scores were captured electronically via a tablet and used a movable point on a 100 mm horizontal scale (0 = no symptoms and 100 = severe symptoms). The tablet automatically quantified the score. The SPEED and VAS were used in conjunction to determine symptomatology at each visit. Corrected visual acuity with habitual correction was measured with a logarithm of the minimum angle of resolution high-contrast chart to determine study eligibility and monitor visual health during the study. A slit-lamp biomicroscope was used to document normal and/or remarkable findings of the anterior eye structures: eyelashes, eyelids, conjunctiva, and cornea. Lid wiper epitheliopathy was graded via a slit-lamp biomicroscope using 10× magnification and external diffuse lighting. Investigators used lissamine green[13] to reveal LWE in the upper eyelid and then graded it using the photographic LWE (PLWE) scale (Figure 1)[13,14] and Korb grading scale (Figure 2).[1] Photo-documentation was car-

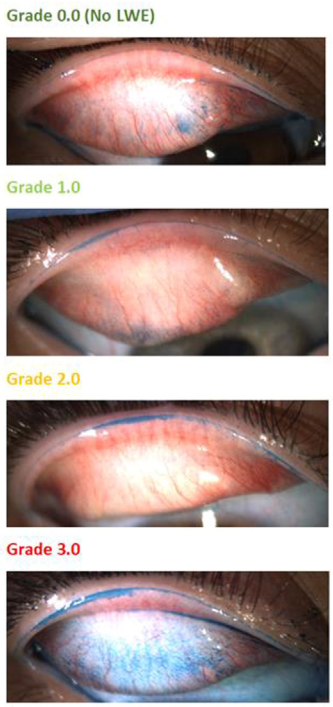

Figure 1. The photographic lid wiper epitheliopathy (LWE) grading scale. Grade 0 = no LWE (only the line of Marx present); grade 1 = slight LWE; grade 2 = moderate LWE; grade 3 = severe LWE. Scores worse than 3.0 were graded as a score of 3.5. Adapted with permission.[15]

* Trademark: MIEBO® (Bausch + Lomb, Bridgewater, New Jersey).
† iLux® (Alcon, Fort Worth, TX, USA).

Step 1: Grading of Horizontal Length of the Lid Wiper staining.

Horizontal Length of Staining	Grade
<2 mm	0
2-4 mm	1
5-9 mm	2
>10 mm	3

Step 2: Grading of Sagittal Height (Width) of the Lid Wiper staining.

Sagittal Height of Staining	Grade
<25%	0
25% - 50%	1
50% - 75%	2
>75%	3

Step 3: Grading of LWE is calculated by taking the average score from steps 1 and 2 above.

Grading Average	Korb LWE Severity Grade
0	No LWE
0.5 – 1.0	Grade 1 LWE
1.5 – 2.0	Grade 2 LWE
2.5 – 3.0	Grade 3 LWE

Figure 2. Three-step process used to grade severity of lid wiper epitheliopathy (LWE) using the Korb et al[1] grading protocol.

ried out using the BI900 LED Slit Lamp with EyeSuite Imaging (Haag-Streit, Bern, Switzerland) to collect representative photos. Lissamine green was eluted from 2 paper impregnated strips (GreenGlo Lissamine Green Ophthalmic Strip; Hub Pharmaceuticals Ltd, Farmington Hills, Michigan) into 50 µL of saline and then 10 µL of dye was micropipetted to the ocular surface; this process was repeated after 1 minute to help ensure a sufficient amount of lissamine green.[15,16]

Participants were randomized across all sites by one unmasked study coordinator to PFHO ophthalmic solution 4 times a day or no treatment in a 1:1 ratio. Perfluorohexyloctane was prescribed 4 times per day as indicated by the manufacturer. A no treatment control group was used in this study to determine if there was an initial effect on LWE and because the only potentially available placebo control treatment would be artificial tears, which is an established treatment for LWE.[17] Treatment was initiated at the baseline/screening visit and persisted throughout the 2-month study. Treatment compliance was monitored with paper diaries during follow-up visits and all participants confirmed adhering to the dosing recommendations. The participants were unmasked and the investigators were masked to the treatment assignments, helping to ensure unbiased recording of LWE. All investigators attended a training session to ensure consistency across procedures in all study sites. Participants were compensated for their time and travel in attending to the study visits.

Sample size and statistical analysis

The primary efficacy variable for this work was the between-group difference in PLWE scale scores at 2 months. Previous work indicated that the mean ± SD severity of LWE score was 1.55 ± 0.44 using the PLWE scale, based on 20 images showing a range of LWE presentations.[14,18] When performing a sample size calculation based upon independent samples with these data, the sample size was 14 participants per group ($\alpha = 0.05$; power = 0.80; effect size = 0.5 units; 2-sample t test). Given the small sample size, 20 participants plus 5 participants per group were recruited to account for potential attrition. This sample size inflation was deemed appropriate to allow for a general understanding of whether LWE improves with treatment compared with control participants.

All data were electronically collected with Research Electronic Data Capture.[19,20] All data were analyzed with Stata/BE 18 (StataCorp LLC, Texas). Lid wiper epitheliopathy changes and comfort comparisons across visits were evaluated with mixed model for repeated measure, and between-group differences by visit were evaluated with unpaired t tests. The mixed model for repeated measure analysis included study outcome, patient, and study visit in the model. Because both eyes were evaluated and required to have LWE, the right eye was designated the study eye; yet, data for both eyes were reported given that it had the potential to provide clinical insights. An additional key outcome of this study was the proportion of participants who had at least a 0.5-unit improvement in the PLWE scores at 2 months compared with the baseline visit. Between-group differences in proportions were evaluated with Fisher exact tests.

Results

This study enrolled 26 participants in each group (Figure 3). The treatment group had a mean ± SD age of 51.6 ± 16.0 years (85% female), whereas the no treatment group had a mean ± SD age of 47.7 ± 15.5 years (73% female). The 2 groups were well matched for age, sex, ethnicity, and race (Table 1; all $P \geq 0.25$). No adverse events were detected via slit-lamp examination or by participant self-report at any visit. Patients in the treatment group reported missing a mean ± SD of 2.8 ± 5.0 drops between the baseline and 2-week visits, 1.7 ± 2.5 drops between the 2-week and 1-month visits, and 3.8 ± 8.0 drops between the 1-month and 2-month visits. Baseline right and left eye visual acuities were well balanced between the 2 groups (Table 1; all $P \geq 0.61$). Visual acuity did not significantly change for either eye for either treatment groups across the study (all $P \geq 0.08$). When evaluating LWE

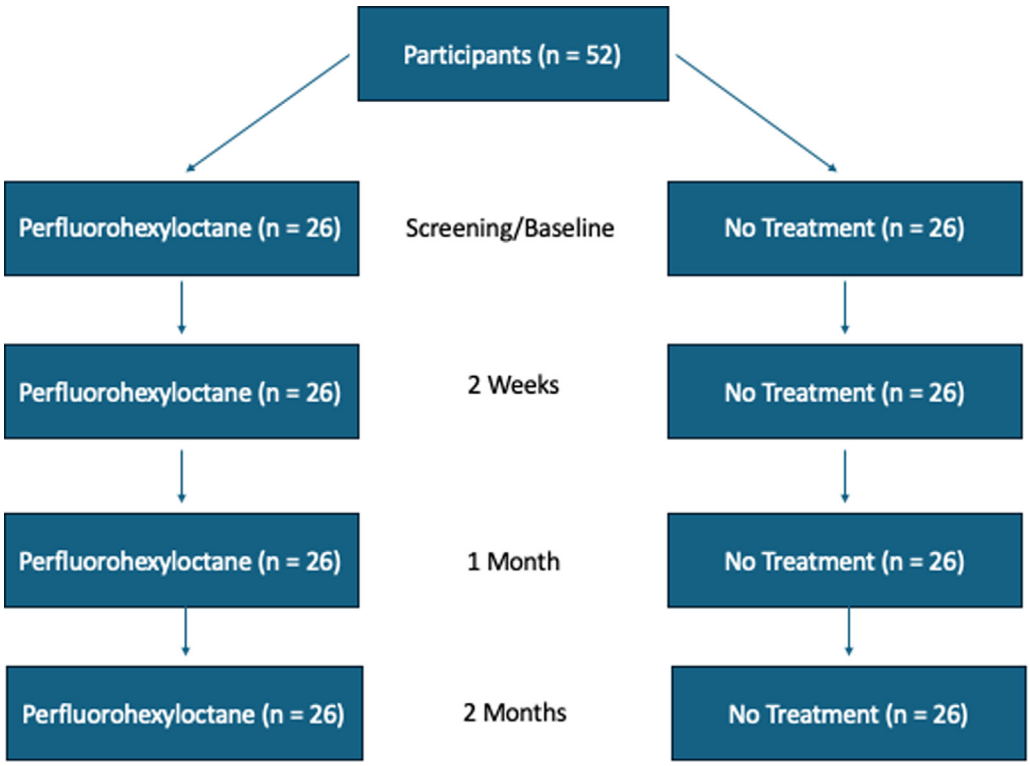

Figure 3. Study flow diagram.

Table 1
Baseline characteristics by participant group.

Metric	Treatment group, n = 26 MIEBO	No treatment group, n = 26 Control	*P* value
Age (y), mean ± SD	51.6 ± 16.0	47.7 ± 15.5	0.40
Female (%)	85	73	0.25
Visual acuity (logMAR), mean ± SD			
Right eye	0.00 ± 0.14	−0.01 ± 0.16	0.61
Left eye	0.00 ± 0.11	−0.05 ± 0.09	0.93
Non-Hispanic (%)	100	96	0.50
Race (%)			
White	80	80	>0.99
Asian	12	12	
Black or African American	8	8	

logMAR = logarithm of the minimum angle of resolution.

severity, SPEED scores, and VAS scores at the baseline visit, the 2 treatment groups were well balanced with no between-group differences (Tables 2 and 3; all $P \geq 0.13$).

When evaluating the groups, the treatment group was significantly more likely to show an improvement of ≥0.5-unit in PLWE scores in right eyes ($P = 0.04$) compared with the no treatment at 2 months compared with baseline. However, there was no significant difference when evaluating left eye between-group differences in improvement of ≥0.5-unit in PLWE scores or in right or left eye improvements of ≥1.0-unit in PLWE scores at 2 months compared with baseline (all $P \geq 0.10$; Table 4). When comparing between groups, mean differences for the PLWE scores were significantly better in the treatment group compared with the no treatment group starting at 2 weeks, and these significant differences between groups remained for the duration of the 2-month study (Table 2; all $P < 0.001$). Photographic LWE scores furthermore improved in the right and left eyes (both $P < 0.001$) of the treatment group over the course of the 2-month study, yet right ($P = 0.003$) but not left ($P = 0.07$) eyes improved in the no treatment group across the 2-month study.

This study also evaluated LWE as graded with the 0 to 3 composite grading scale by Korb et al.[1,12] When evaluating the groups, the treatment group was significantly more likely to show an improvement of ≥0.5-unit or ≥1.0-unit in LWE scores in left eyes ($P \leq 0.04$) compared with the no treatment at 2 months compared with baseline. However, there was no significant difference when evaluating right eye between-group differences in improvement of ≥0.5-unit or ≥1.0-unit in LWE scores at 2 months compared with baseline (all $P \geq 0.08$; Table 4). When comparing between-group mean differences for the Korb et al.[1] LWE scale, scores were significantly better in the treatment group compared with the no treatment group starting at 2 weeks, and the significant between-group difference remained for the duration of the study (Table 1; all $P < 0.001$). Lid wiper epitheliopathy scores furthermore improved in the right and left eyes in both group over the course of the 2-month study (all $P \leq 0.03$). Figure 4 shows representative images of the improvement on LWE severity noticed in a participant using PFHO at baseline before treatment and at the 2-month visit.

This study furthermore evaluated a variety of ocular symptom scores. When evaluating SPEED scores, there was a significant dif-

Table 2
Between-group comparisons of lid wiper epitheliopathy scores by visit and by scale for each eye.

Metric	Baseline (Mean ± SD)			2 wk (Mean ± SD)			1 mo (Mean ± SD)			2 mo (Mean ± SD)		
	Treatment	No treatment	*P* value	Treatment	No treatment	*P* value*	Treatment	No treatment	*P* value*	Treatment	No treatment	*P* value*
Lid wiper epitheliopathy, right eye (Korb scale: 0–3)	1.50 ± 0.65	1.71 ± 0.67	0.13	0.81 ± 0.60	1.60 ± 0.69	**<0.001**	0.75 ± 0.59	1.44 ± 0.96	**0.002**	0.60 ± 0.55	1.37 ± 0.80	**<0.001**
Lid wiper epitheliopathy, left eye (Korb scale: 0–3)	1.62 ± 0.74	1.65 ± 0.81	0.43	0.83 ± 0.53	1.52 ± 0.74	**<0.001**	0.58 ± 0.50	1.46 ± 0.76	**<0.001**	0.63 ± 0.61	1.33 ± 0.94	**0.001**
Photographic lid wiper epitheliopathy, right eye (scale: 0.0–3.5)	1.58 ± 0.77	1.83 ± 0.81	0.13	0.73 ± 0.57	1.94 ± 0.83	**<0.001**	0.67 ±.065	1.54 ± 1.03	**<0.001**	0.58 ± 0.44	1.44 ± 0.95	**<0.001**
Photographic lid wiper epitheliopathy, left eye (scale: 0.0–3.5)	1.58 ± 0.78	1.67 ± 0.85	0.34	0.79 ± 0.49	1.54 ±0.78	**<0.001**	0.54 ± 0.47	1.56 ± 0.79	**<0.001**	0.62 ± 0.53	1.37 ± 1.04	**<0.001**

* Values are significant; between-group *P* values were determined with unpaired *t* tests.

Table 3
Between-group comparisons of ocular symptomatology questionnaires by study visit.

Question	Baseline (Mean ± SD)			2 wk (Mean ± SD)			1 mo (Mean ± SD)			2 mo (Mean ± SD)		
	Treatment	No treatment	*P* value	Treatment	No treatment	*P* value*	Treatment	No treatment	*P* value*	Treatment	No treatment	*P* value*
Standard Patient Evaluation of Eye Dryness (0–28 scale)	12.8 ± 4.5	12.2 ± 3.6	0.70	7.6 ± 3.3	10.4 ± 4.1	**0.005**	7.0 ± 3.4	10.5 ± 4.0	**0.001**	5.7 ± 3.3	9.8 ± 3.0	**<0.001**
Eye dryness symptom feels at this moment (0–100 scale)†	45.8 ± 30.5	51.6 ± 23.8	0.23	24.2 ± 23.6	48.3 ± 25.0	**<0.001**	26.6 ± 31.7	49.7 ± 27.1	**0.003**	17.1 ± 18.4	41.8 ± 26.5	**<0.001**
Eye scratchiness symptom feels at this moment (0–100 scale)†	32.8 ± 27.0	31.1 ± 25.0	0.59	16.1 ± 18.8	30.6 ± 26.5	**0.01**	16.8 ± 22.5	31.1 ± 24.8	**0.02**	11.1 ± 14.7	25.0 ± 23.9	**0.008**
Eye gritty/sandy Feeling symptom feels at this moment (0–100 scale)†	34.9 ± 29.0	31.6 ± 26.4	0.67	17.6 ± 21.3	30.8 ± 27.1	**0.03**	14.6 ± 23.9	27.9 ± 27.2	**0.03**	10.7 ± 16.3	25.0 ± 24.3	**0.008**
Eye irritation/soreness symptom feels at this moment (0–100 scale)†	33.0 ± 28.3	21.0 ± 21.3	0.95	20.6 ± 21.0	21.9 ± 24.4	0.42	14.6 ± 20.5	21.7 ± 21.4	0.11	12.2 ± 16.4	24.7 ± 22.6	**0.01**
Eye burning symptom feels at this moment (0–100 scale)†	30.8 ± 29.3	18.4 ± 22.5	0.95	18.9 ± 22.8	20.3 ± 25.6	0.42	11.6 ± 19.9	21.5 ± 26.4	0.07	6.1 ± 14.8	18.4 ± 19.8	**0.007**
Eye stinging symptom feels at this moment (0–100 scale)†	28.9 ± 29.7	12.3 ± 16.2	0.99	15.0 ± 25.6	17.1 ± 22.4	0.38	10.7 ± 19.3	18.5 ± 24.8	0.11	6.2 ± 14.9	14.8 ± 19.1	**0.04**
Eye watering symptom feels at this moment (0–100 scale)†	31.8 ± 25.6	23.9 ± 24.3	0.87	18.3 ± 20.7	30.9 ± 27.5	**0.03**	12.3 ± 17.4	30.8 ± 29.8	**0.004**	9.7 ± 14.1	21.7 ± 23.5	**0.01**
Eye fatigue symptom feels at this moment (0–100 scale)†	34.7 ± 28.9	27.4 ± 26.8	0.83	12.4 ± 22.7	27.4 ± 27.2	**0.02**	10.4 ± 18.2	31.0 ± 26.0	**0.001**	10.1 ± 19.3	33.1 ± 27.1	**0.001**
Eye itching symptom feels at this moment (0–100 scale)†	25.4 ± 24.7	24.0 ± 30.3	0.57	12.5 ± 18.3	27.4 ± 29.3	**0.02**	11.3 ± 20.0	30.8 ± 26.4	**0.002**	12.3 ± 18.2	27.7 ± 23.3	**0.006**
Current eye discomfort symptom feels at this moment (0–100 scale)†	40.0 ± 25.7	35.2 ± 24.2	0.76	27.2 ± 21.3	32.5 ± 23.1	0.19	22.7 ± 24.0	41.7 ± 24.6	**0.003**	19.2 ± 18.4	38.5 ± 23.8	**0.001**

* Bold values are significant; between-group *P* values were determined with unpaired *t* tests.
† Visual analog scale with no symptoms = 0 and severe symptoms = 100.

Table 4
Categorical change in lid wiper epitheliopathy scores by eye.

Scale	Treatment			No treatment		
	≥0.5-unit change	≥1.0-unit change	Worsening	≥0.5-unit change	≥1.0-unit change	Worsening
Right eye						
Korb et al.[1] scale	76.9%	61.5%	0.0%	50.0%	34.6%	15.4%
Photographic lid wiper epitheliopathy scale[14]	81%	57.7%	0.0%	50.0%	42.3%	15.4%
Left eye						
Korb et al.[1] scale	76.9%	53.8%	<0.1%	34.6%	26.9%	19.2%
Photographic lid wiper epitheliopathy scale[14]	65.4%	50.0%	0.0%	38.5%	26.9%	19.2%

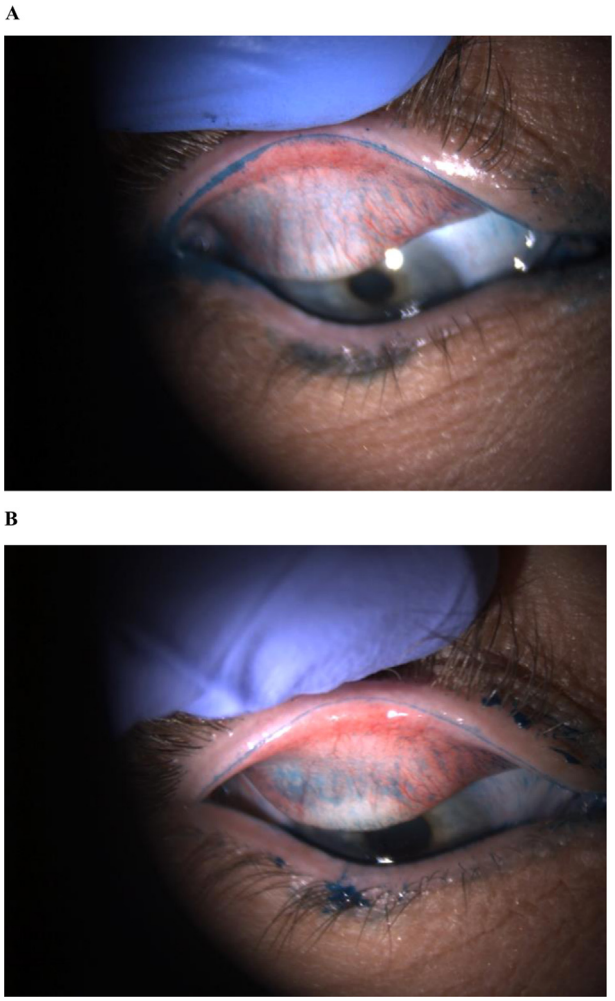

Figure 4. Representative images from 1 patient of the clinical improvement on lid wiper epitheliopathy severity noticed (A) at baseline and after using perfluorohexyloctane (B) at the 2-month visit.

ference between the treatment and no treatment group starting at 2 weeks ($P = 0.005$), and this significant difference remained for the duration of the study (all $P \leq 0.001$; Table 3). Standard Patient Evaluation of Eye Dryness scores likewise were significantly better in both group at the 2-month visit compared with the baseline visit ($P < 0.001$). When evaluating the proportion of participants who had an improvement in VAS scores, a high percentage of participants in the treatment group versus the no treatment group had a clinically meaningful improvement in eye dryness (69% vs 54%), eye scratchiness (62% vs 38%), eye gritty/sandy feeling (58% vs 42%), eye irritation/soreness (58% vs 35%), eye burning (65% vs 42%), eye stinging (58% vs 19%), eye watering (62% vs 35%), eye fatigue (65% vs 42%), eye itching (46% vs 27%), and current eye discomfort (62% vs 38%) VAS scores. All VAS scores were significantly different between the 2 groups at the 2-month visit (all $P \leq 0.04$; Table 2). The treatment group ($P \leq 0.01$) had a significant improvement in all VAS scores across the 2-month study. The no treatment group had a significant improvement in eye dryness VAS scores across the 2-month study ($P = 0.04$); yet, no other VAS scores in the no treatment group changed across the study (all $P \geq 0.14$).

Discussion

Lid wiper epitheliopathy has been described as a microtrauma caused by inadequate ocular lubrication and/or excessive friction,[4] and it has been established as a diagnostic sign of DED.[1,15] Recently, PFHO has been approved by the US Food and Drug Administration for the treatment of signs and symptoms of DED, and pivotal clinical studies have reported its efficacy and safety in patients with meibomian gland disease associated with mild-to-moderate DED.[21–26] Although PFHO is a relatively new drug that may not be available or affordable in every market, the present study determined that PFHO significantly improved LWE signs as measured with both the Korb and PLWE scales while significantly improving symptoms compared with no treatment.

Ballesteros-Sánchez et al[27] conducted a systematic review of the efficacy and safety of PFHO and concluded that its use improves DED signs and symptoms and has a high patient satisfaction. These improvements were evident in several key outcomes reported in previous investigations including DED symptomology and signs including tear break up times, lipid layer thickness, total corneal fluorescein staining, Schirmer test, and meiboscore (meibomian gland atrophy).[28–30] However, none of the previous investigations specifically explored the friction reducing properties of PFHO in participants with LWE.[31]

First, the results of the present study found that the treatment group had a statistically significant improvement in LWE severity at the 2-week visit compared with the no treatment group and this difference remained for the 2-months duration of this study. This improvement was noted using both grading scales currently available to clinicians; one based on a photographic scale of LWE (PLWE) and the other based on Korb composite score of the width and length of LWE staining. These scales were used to evaluate both right and left eyes, and when doing so, they yielded similar but numerically slightly different results suggesting that there may be clinical value in evaluating both eyes in both trials and the clinical setting. Furthermore, to determine the effect of PFHO on DED symptomatology, participants were monitored using the SPEED questionnaires and 10 VAS questions to fully characterize DED symptom severity. At baseline, the average DED symptomatology scores for both the treatment and control groups indicated moderate DED (SPEED scores of 12.8 ± 4.5 and 12.2 ± 3.6 for the treatment and control groups, respectively).[10] Both groups had a significant improvement in SPEED questionnaire scores, and the treatment group had a significant improvement in all VAS scores on study completion. It is worth noting that the between-group improvement in DED symptomatology measured

using SPEED questionnaire was already evident by the 2-week visit, which is consistent with the pivotal trial data. In contrast, symptomatology in the no treatment group only had improvements in SPEED and eye dryness VAS scores across the study, and these improvements were all significantly less than those experienced by the treatment group.

No adverse events were reported with the use of PFHO, which can likely be at least partially attributed to PFHO being preservative-free. All participants (100%) self-reported adherence to the dosage instructions in the active group with a relatively low mean number of missed drops being reported. Therefore, this study reports effectiveness of PFHO ophthalmic solution as a novel treatment in reducing LWE and DED symptoms. Because LWE is a relatively new clinical sign,[1] few therapeutic strategies have been evaluated. Nevertheless, Itakura et al[32] reported improvement of LWE in a case study with 2 patients who were treated with rebamipide 4 times per day. Itakura et al[32] specifically found that both eyelid and corneal staining were remarkably improved in both cases. More recently, Guthrie et al[17] investigated the impact of using Systane Balance Lubricant Eye drops (Alcon, Fort Worth, Texas) or a nonlipid containing contact lens rewetting drop up to 4 times per day in symptomatic contact lens wearers. The authors overall reported increased comfortable wearing time and reduced signs of LWE at 1-month compared with baseline in the treatment group and in the treatment group compared with the control group at the 1 month visit. None of these studies compared products to PFHO; thus, further research is needed to determine if one treatment is better than another for treating LWE in participants who suffer from symptomatic DED.

In this study, all investigators were masked to the participant's group and data were collected in a diverse set of locations across the United States. Nevertheless, a potential limitation of this study is that enrolled participants were not masked to their treatment group. Specifically, participants in the control group did not receive an active treatment. This study design was deemed necessary because this study only had access to commercially available options such as artificial tears, which likely would also have a treatment effect on DED symptomatology.[31,33] Because PFHO has no vehicle, this study opted to use no treatment as the control to determine the true potential magnitude of treatment that could be expected from treating LWE in participants with DED with PFHO. A limitation of this approach is that a possibility exist that this affected the responses when completing the symptomatology questionnaires because of the Hawthorn effect.[34] Despite this limitation, the significant effect observed in the masked evaluation of LWE signs at 2-weeks and beyond in the treatment group but to a lesser degree in the control group, which was the main and novel aspect of this study, seems to corroborate the symptomatology findings. Future independent investigations are necessary to confirm the initial promising findings reported in this study. These investigations might consider monitoring participants during a larger, randomized, masked study with a longer follow-up and to compare the effects of PFHO on LWE with other more economical treatment options such as artificial tears or other topical ophthalmic drugs to gain additional information regarding the long-term benefits of this treatment. These larger studies might likewise provide insights into what type of patient would be the ideal patient with LWE to treat with PFHO.

Conclusions

This study indicates that PFHO administered 4 times a day appears to be beneficial for reducing LWE signs and DED symptoms starting as soon as 2 weeks after beginning treatment compared with a no treatment control and when compared with baseline values. Given that the PFHO was found to be safe in this study and others,[35] further independent research should further evaluate the benefits of this novel treatment compared with other available strategies such as artificial tears or even topical drugs such as cyclosporine or lifitegrast eye drops in the management of DED symptomatology, especially when LWE is present. To address the present study's limitation, future work should also evaluate longer, larger, masked, randomized studies to report longer-term treatment effects.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Chris Lievens reports financial support was provided by Bausch & Lomb Americas Inc. Chris Lievens reports a relationship with Bausch & Lomb Americas Inc that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

All authors have approved the final article version. Chris Lievens and Andrew D. Pucker were responsible for study conception and design. Chris Lievens, Stephen M. Montaquila, Brad Giedd, and Gina Wesley performed data acquisition. Chris Lievens, Andrew D. Pucker, and Marta Vianya-Estopa performed data analysis and interpretation. Chris Lievens, Andrew D. Pucker, Zackarias Coker, John Meyers, and Marta Vianya-Estopa wrote and edited the manuscript draft. Chris Lievens, Andrew D. Pucker, Quentin Franklin, Morgan Bromley, Zackarias Coker, and John Meyers were responsible for study administration and coordination.

Data Availability

The confidential source data are available upon request due to privacy/ethical restrictions.

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