



## Original Article

# Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment

Jack V Greiner DO PhD<sup>1,2</sup>

<sup>1</sup>Schepens Eye Research Institute, The Massachusetts Eye and Ear Infirmary and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA and <sup>2</sup>Boston Ocular Surface Center, Boston and Winchester, Massachusetts, USA

### ABSTRACT

**Purpose:** To determine the 1-year post-treatment dry eye status of subjects with meibomian gland dysfunction and dry eye symptoms after receiving a single LipiFlow Thermal Pulsation System treatment.

**Design:** Single-centre, prospective, observational, open-label, 1-month-registered clinical trial with a 1-year follow-up examination.

**Participants:** Patients with evaporative dry eye disease with meibomian gland dysfunction and dry eye symptoms who had participated in the registered 1-month clinical trial.

**Methods:** Eighteen of 30 subjects initially enrolled were able to return for a 1-year follow-up. Both eyes of all patients were treated with a single 12-min treatment using the LipiFlow Thermal Pulsation System. Meibomian gland function, tear break-up time and dry eye symptoms were measured. Data are presented for pretreatment (baseline), and 1-month and 1-year post-treatment.

**Main Outcome Measures:** Meibomian gland secretion scores, and tear break-up time and dry eye symptoms.

**Results:** Significant improvement in meibomian gland secretion scores from baseline measurements ( $4.0 \pm 3.4$ ) to 1-month post-treatment ( $11.3 \pm 4.7$ ;  $P < 0.0005$ ) was maintained at 1-year ( $7.3 \pm 4.6$ ;  $P < 0.05$ ). Baseline tear break-up time ( $4.9 \pm 3.0$ ) was significantly increased at 1-month ( $9.5 \pm 6.9$ ;  $P < 0.05$ ); however, this improvement was no longer evident at 1-year post-treatment ( $6.0 \pm 4.4$ ). The significant improvement in symptom scores on Ocular Surface Disease Index and Standard Patient Evaluation of Eye Dryness questionnaires observed at 1-month ( $P < 0.0005$ ) was maintained at 1-year (Ocular Surface Disease Index [ $P < 0.05$ ]; Standard Patient Evaluation of Eye Dryness [ $P < 0.0005$ ]).

**Conclusion:** A single 12-min treatment with the LipiFlow Thermal Pulsation System offers an effective treatment for evaporative dry eye and meibomian gland dysfunction resulting in significant and sustained improvement in signs and symptoms for up to 1 year.

**Key words:** dry eye, LipiFlow thermal pulsation system, meibomian gland dysfunction.

■ **Correspondence:** Dr Jack V Greiner, Boston Ocular Surface Center, 955 Main Street, Suite 307, Winchester, MA 01890-1961, USA. Email: greiner@schepens.harvard.edu

Received 6 June 2012; accepted 1 November 2012.

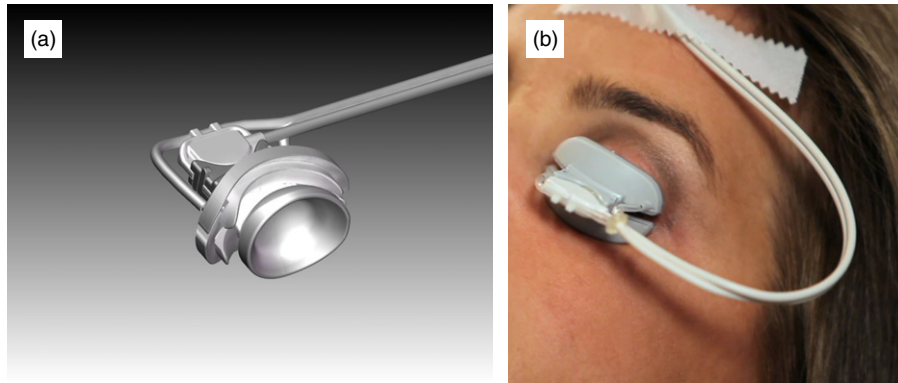
Competing/conflicts of interest: No stated conflict of interest.

Funding sources: Valerie and Walter Winchester Grant, Boston Ocular Surface Center, Boston and Winchester, MA, USA, and TearScience, Inc., Morrisville, NC, USA.

This study was presented in part at the American Society of Cataract and Refractive Surgery Symposium on Cataract, IOL and Refractive Surgery, April 29, 2011, San Diego, CA, USA.

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**Figure 1.** (a) The LipiFlow device. The device consists of two main components: an insulated lid warmer resembling a scleral contact lens that vaults the cornea and provides precision controlled heat to the tissues of the internal eyelid, and an eye cup comprised of an upper and lower inflatable air bladder that pulsates to express the meibomian glands. (b) The LipiFlow device positioned on the eye for treatment with the LipiFlow Thermal Pulsation System (LTPS). As the air bladders are inflated the upper and lower eyelids are compressed between these bladders and the lid warmer, as the air bladders pulse the LTPS sequentially inflates and deflates messaging the eyelids and thus the meibomian glands in a proximal to distal (orifice) direction.

## INTRODUCTION

Historically, the treatment of evaporative dry eye has been focused on emulating and fortifying the precorneal tear film, with considerable effort on developing artificial tear formulations that mimic the aqueous and mucus components of the tear film. Such formulations, however, offer limited relief and require frequent dosing. Recently, however, the discovery of an oil-in-water technology<sup>1</sup> and the eventual development of oil-in-water emulsion-based artificial tears (Soothe XP, Bausch & Lomb, Rochester, NY, USA; Systane Balance, Alcon Pharmaceuticals, Fort Worth, TX, USA) has radically extended the duration of action of tear supplements, such that relief can be measured in terms of hours rather than minutes.<sup>2</sup>

As an alternative to the exogenous enrichment of the tear film, attempts have been made to address underlying ocular pathology that may ultimately manifest as, or contribute to, evaporative dry eye – the theory being that restoration of function will lead to significantly longer periods of relief. In this regard, the meibomian glands are logical targets for therapeutic intervention given the increasing recognition of the role of these glands and their lipid contents in maintaining the integrity of the tear film.<sup>3–8</sup> In fact, meibomian gland dysfunction (MGD) secondary to meibomian gland obstruction is currently considered the most prevalent aetiology of dry eye symptoms.<sup>9</sup> The recent introduction of the LipiFlow Thermal Pulsation System (LTPS) (TearScience, Inc., Morrisville, NC, USA)<sup>10,11</sup> provides, for the first time, a controlled method to express obstructed meibomian glands by applying heat to the upper and lower palpebral conjunctival surfaces while simultaneously applying pulsatile

**Table 1.** Patient demographics ( $n = 18$ )

Gender, $n$ (%)	
Male	4 (22%)
Female	14 (78%)
Age (years), mean (standard deviation)	63.2 (12.1)
Race, $n$ (%)	
Asian	0
Black	0
Caucasian	18 (100%)
Other	0

pressure to cutaneous eyelid surfaces (Fig. 1). Furthermore, a single 12-min treatment has been reported to significantly improve the meibomian gland secretion (MGS) score, tear film break-up time (TBUT) and symptoms scores when measured at 1 month<sup>12</sup> and 9 months<sup>13</sup> post-treatment. No other treatment modality has been reported to provide such sustained relief from evaporative dry eye signs and symptoms following a single treatment.

The present report summarizes the meibomian gland and dry eye status of a subcohort of 18 patients evaluated 1 year after a single treatment with the LTPS.

## METHODS

A subcohort of patients (Table 1) who participated in a multicentre registered 1-month LipiFlow clinical trial<sup>12</sup> in March and April of 2009 at the Winchester site of the Boston Ocular Surface Center was examined by the same clinical investigator (JVG) 1 year after receiving the single LTPS treatment. As in the original multicentre clinical trial study inclusion required a score of  $\geq 6$  in a Standard Patient Evaluation of Eye Dryness (SPEED) that assessed

**Table 2.** Best-corrected visual acuity (ETDRS) ( $n = 18$ )

Mean (SD) LogMAR values	OD	OS
Baseline	0.01 (0.07)	0.00 (0.07)
1-Month	0.01 (0.08)	0.01 (0.09)
12-Month	0.08 (0.11)	0.08 (0.12)

ETDRS, early treatment diabetic retinopathy study; LogMAR, logarithm of minimum angle of resolution; OD, right eye; OS, left eye; SD, standard deviation.

frequency and severity of dryness, grittiness, scratchiness, soreness, irritation, burning, watering and eye fatigue within 3 months prior to examination. Additionally, qualifying subjects had evidence of meibomian gland obstruction that was based on an MGS score of  $\leq 12$  for a total of 15 glands of the lower eyelid. Ophthalmologic examinations included history, best-corrected visual acuity (Table 2), slit-lamp biomicroscopy and ophthalmoscopy. These examinations were performed at 1-year post-LTPS treatment by the investigator without access to source documents or the completed case report forms of the multicentre clinical trial.<sup>12</sup>

Of the original subjects enrolled at the Winchester site of the Boston Ocular Surface Center ( $n = 30$  subjects) 1-month LipiFlow clinical trial, 18 patients were available for voluntary follow-up examination at 1 year. The 12 patients lost to follow-up can be grouped into the following categories: (i) those that no longer felt the need to participate as they now considered themselves asymptomatic as a result of their original thermal pulsation treatment; (ii) those that were either unwilling or unable to commit to the time obligation inherent in this follow-up evaluation; (iii) those that had relocated since the initial study 1 year prior; and (iv) those that could not be contacted despite considerable efforts. Despite this decrease in the number of patients available for follow-up examination, the dry eye profile of this subcohort evaluated at 12 months was remarkably similar to the larger cohort of subjects ( $n = 30$ ) from the initial multicentre clinical study.<sup>12</sup> The main objective measures were the same as those from the 1-month LipiFlow clinical trial: meibomian gland assessment, TBUT and dry eye symptoms as measured by the Ocular Surface Disease Index (OSDI)<sup>14</sup> and SPEED<sup>15</sup> questionnaires. Subjects were queried regarding their use of lubricating eye drops, systemic medicants or warm compresses, and none of the subjects reported more than occasional use of lubricating eye drops.

### Inclusion criteria

Inclusion criteria for the registered LipiFlow clinical trial have been previously reported.<sup>12</sup> These

criteria included consenting subjects:  $\geq 18$  years of age, willingness to comply with the study procedures and schedule, reported dry eye symptoms within 3 months of the baseline examination, have a SPEED<sup>15</sup> score  $\geq 6$  at the baseline visit, and evidence of meibomian gland obstruction in the lower eyelid with a total MGS score of  $\leq 12$  for 15 glands evaluated.

### Exclusion criteria

Exclusion criteria for the registered LipiFlow clinical trial have been previously reported.<sup>12</sup> These criteria excluded subjects with: evidence of coexisting ocular conditions in either eye posing potential increased risk of procedure-related injury, coexisting ocular or systemic conditions that might limit the effectiveness of treatment with the LipiFlow device, and for coexisting conditions that potentially could interfere with safety and effectiveness assessments of the treatment.

### Study design

This subcohort of 18 subjects (36 eyes) had received a single 12-min in-office LTPS treatment at a single study site as part of a larger, multicentre study.<sup>12</sup> Baseline measurements of dry eye signs and symptoms of all 18 patients (36 eyes) were recorded prior to LTPS treatment and repeated at 2 and 4 weeks post-treatment as part of the multicentre trial. For presentation of the data reported herein, this post-treatment group will be referred to as the 1-month study/data. The subcohort in the present study was similarly evaluated at 1 year in the absence of any further LTPS treatment or any other reported treatment other than occasional use of tear adjuvants, although the use of such adjuvants was prohibited on the day of evaluation.

### Study parameters

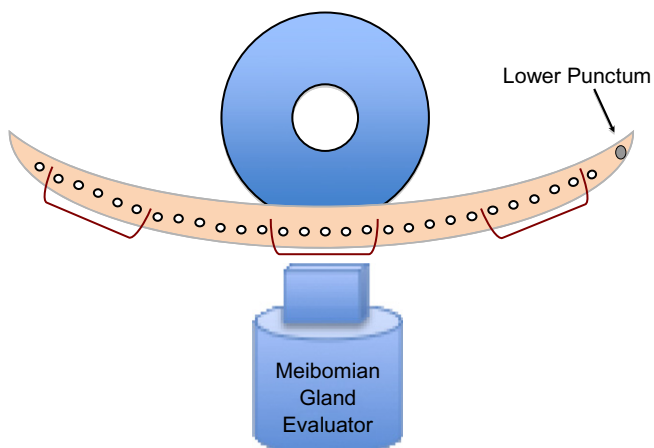
The outcome measures used to evaluate the long-term effectiveness of the LTPS treatment over the 1-year period were dry eye symptoms using two different questionnaires, TBUT and meibomian gland assessment.

Dry eye symptoms were assessed using results from both the OSDI<sup>14</sup> and the SPEED<sup>15</sup> questionnaires. The OSDI questionnaire assessed the subject's frequency and severity of dry eye symptoms in specific contexts (e.g. while using a computer, while driving) during the week prior to the examination. The SPEED questionnaire assessed both the frequency and severity of dry eye symptoms, including dryness, grittiness, scratchiness, soreness, irritation, burning, watering and eye fatigue (i.e. symptoms not

related to any specific context) during the 3 months prior to examination.

TBUT was performed using the dry eye test (DET) method.<sup>16</sup> This method uses a fluorescein-impregnated DET strip (Amcon Laboratories, St. Louis, MO, USA). The size and shape of the fluorescein-impregnated portion of the DET strip provides a significant reduction in sensation when applied to the eye, improved single measurement reliability and enhanced measurement precision compared with a conventional fluorescein strip.<sup>16,17</sup> TBUT was measured with a stopwatch with an accuracy of a tenth of a second and an average of three readings were used for data analysis.

Meibomian gland assessment was standardized using a handheld instrument (meibomian gland evaluator applying approximately 1.2 g/mm<sup>2</sup> pressure along the distal eyelid subjacent to the eyelash line).<sup>18</sup> The meibomian gland evaluator was oriented such that the longest dimension of the tip was positioned adjacent and coincident to the horizontal plane. Meibomian glands were evaluated along the lower eyelid margin, consisting of five consecutive glands located in each of the temporal, central and nasal regions (Fig. 2). The characteristics of the expressed gland contents were graded on a scale of 0–3, where 0 = no secretion, 1 = inspissated/filamentary secretion, 2 = cloudy liquid secretion and 3 = clear liquid secretion. The sum of the grades for all 15 glands determined the total MGS score (range 0–45); as such, the MGS score represents both the number of secreting meibomian glands and the quality of those secretions.



**Figure 2.** Schematic of the right lower eyelid with the meibomian gland evaluator (MGE) positioned on the skin of the central eyelid subjacent to the anterior eyelid margin. With engagement of the MGE with the skin, pressure is applied to the distal portion of the eyelid skin and the secretion characteristics of five consecutive meibomian glands in each of three regions (temporal, central, nasal) are observed and graded.

## Statistical analysis

SPSS software (IBM Corp, Somers, NY, USA) and GraphPad Prism (GraphPad Software, La Jolla, CA, USA) were used to perform statistical analysis. Analysis and descriptive changes from baseline (pre-LipiFlow procedure levels), 1-month levels and 1-year levels in dry eye symptoms, TBUT and meibomian gland assessment were made using repeated-measures analysis of variance with Bonferroni-corrected post-hoc testing and descriptive statistics. The baseline, 1-month post-treatment values and 1-year values for the subcohort in the present study were calculated from the data for these specific subjects in the original multicentre study.<sup>12</sup> A statistically significant difference was based on the level  $\alpha = 0.05$ .

## RESULTS

Treatment with the LipiFlow® thermal pulsation device resulted in a significant improvement in signs and symptoms from baseline measurements to 1-month post-treatment, and these improvements persisted through 12 months with the exception of TBUT which regressed to near baseline values. No statistically significant difference was found between right and left eyes, therefore the results of right and left eyes were averaged. Additionally, since this is an extension of a previous study reporting data at 9-months post-treatment,<sup>13</sup> the graphs presented herein include this prior 9-month data for this specific cohort as an additional reference point.

### MGS score

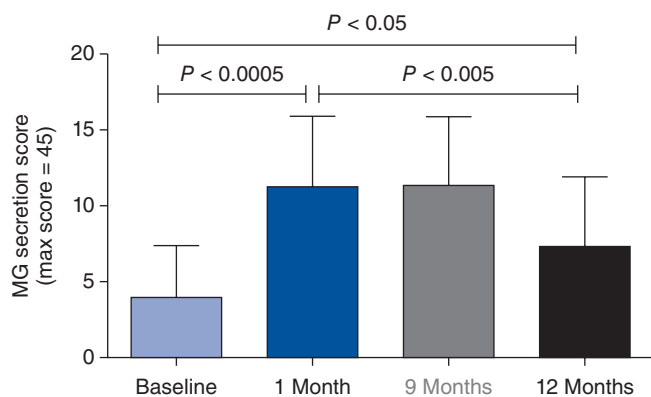
The MGS score significantly increased from pre-procedure levels ( $4.0 \pm 3.4$ ) to postprocedure at 1-month ( $11.3 \pm 4.7$ ,  $P < 0.0005$ ) and this improvement was maintained at 1-year from baseline ( $7.3 \pm 4.6$ ,  $P < 0.05$ ) (Fig. 3).

### TBUT

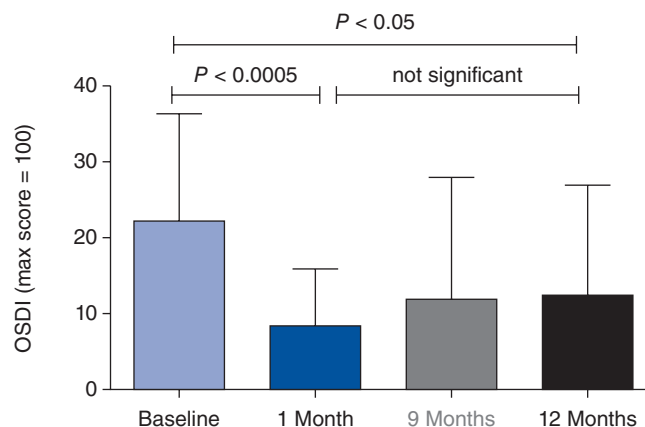
There was a statistically significant increase in TBUT from the preprocedure ( $4.9 \pm 3.0$ ) to the 1-month postprocedure visit ( $9.5 \pm 6.9$ ,  $P < 0.05$ ). There was a significant decline in TBUT from 1-month postprocedure to 1-year ( $6.0 \pm 4.4$ ,  $P < 0.05$ ). At the 1-year visit the TBUT had regressed to preprocedure baseline levels ( $P > 0.05$ ) (Fig. 4).

### OSDI score

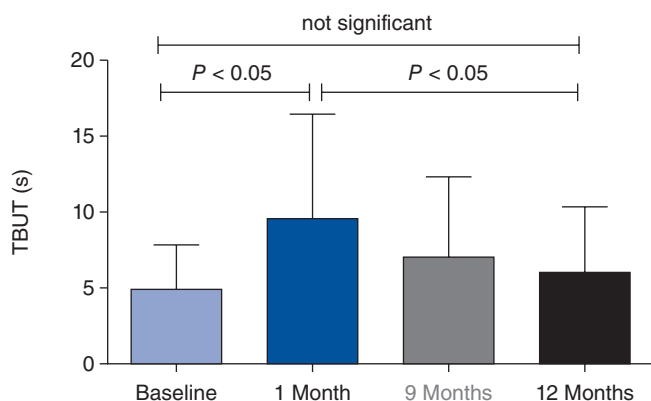
There was significant improvement in OSDI symptom score at 1 month ( $8.5 \pm 7.5$ ) compared to the preprocedure levels ( $22.2 \pm 14.2$ ;  $P < 0.0005$ ).



**Figure 3.** The mean meibomian gland (MG) secretion scores from the 15 meibomian test glands of the lower eyelid measured at pretreatment baseline and 1-month and 1-year post-treatment with the LipiFlow Thermal Pulsation System. Nine-month time point (mean = 11.3 ± 4.6 standard deviation) from a previous study by the author<sup>13</sup> is included for reference purposes.



**Figure 5.** The mean Ocular Surface Disease Index (OSDI)<sup>14</sup> at pretreatment baseline and 1-month and 1-year post-treatment with the LipiFlow Thermal Pulsation System. Nine-month time point (mean = 12.0 ± 16.0 standard deviation) generated from a prior study.<sup>13</sup>



**Figure 4.** The mean tear break-up time (TBUT) measured at pretreatment baseline, and 1-month and 1-year post-treatment with the LipiFlow Thermal Pulsation System. Nine-month time point (mean = 7.2 ± 6.1 standard deviation) generated from a prior study.<sup>13</sup>

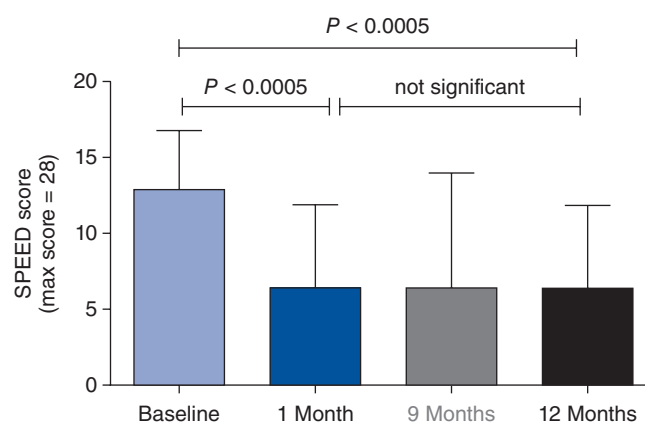
The improvement in OSDI scores from preprocedure levels was maintained at the 1-year visit (12.4 ± 14.6,  $P < 0.05$ ) (Fig. 5).

### SPEED score

There was a significant improvement in SPEED scores at the 1-month visit (6.4 ± 5.5) compared to the preprocedure scores (12.9 ± 3.8;  $P < 0.0005$ ). The improvement in SPEED scores from preprocedure levels was maintained at the 1-year visit (6.3 ± 5.5,  $P < 0.0005$ ) (Fig. 6).

### DISCUSSION

A single, 12-min treatment with the LTPS is a highly efficacious intervention for the treatment of MGD



**Figure 6.** The mean Standard Patient Evaluation of Eye Dryness (SPEED)<sup>15</sup> score measured at pretreatment baseline, and 1-month and 1-year post-treatment with the LipiFlow Thermal Pulsation System. Nine-month time point (mean = 6.4 ± 7.6 standard deviation) generated from a prior study.<sup>13</sup>

secondary to meibomian gland obstruction. Previous reports on both the original multicentre trial<sup>12</sup> and a subcohort ( $n = 21$ ) of the original trial at 9 months<sup>13</sup> have demonstrated significant improvement in signs and symptoms of dry eye at 1 month and 9 months following a single LTPS treatment. The fact that a single LTPS treatment improves meibomian gland function and reduces symptoms for up to 9 months establishes a prolonged duration of action. The present study extends these earlier observations by documenting that some improvements persist up to 1 year post-treatment. The magnitude of the degree of improvement at 1-year post-treatment would have disqualified over 60% (11) of the 18 subjects from entering the original multicentre study based on the inclusion criteria.

Evaluating this subcohort at multiple time points during this 1-year post-treatment period provided an opportunity to address two questions beyond the issue of duration of improvement: (i) what is the pattern of symptom regression, that is, which dry eye parameters are the first to exhibit a significant return to the pretreatment levels that were associated with MGD; and (ii) does the data provide any guidance as to an appropriate timeframe for LTPS re-treatment. With regard to the first question, it is instructive to examine the TBUT parameter and its potential implications. Subjects in this subcohort enjoyed a significant improvement in TBUT through the 9-month post-treatment time point. Although the absolute value of the mean TBUT decreased over 9 months, this change was not statistically significant.<sup>13</sup> By the 12-month evaluation, however, these values had essentially returned to pretreatment levels. No other sign or symptom measured in this study returned to baseline values at the 1-year time point. This suggests that changes in the stability of the precorneal tear film may be the first indicator of a potential disruption to, and/or within, the meibomian gland system before overt signs of meibomian gland obstruction become grossly evident and prior to significant symptomatic presentation on the part of the patient. Identifying the nature and source of these tear film 'destabilizers' may provide clues to elucidate the initial stages of the sequence of events that ultimately manifest as MGD/meibomian gland obstruction.

Under ideal conditions, therapeutic intervention should take place before a physiological system is so compromised that functionality is significantly impacted as evidenced by symptom severity and/or tissue damage. The present study suggests that there is a window of opportunity for re-treatment with LTPS before meibomian glands revert to an overtly obstructed stage. At 1-year post-treatment, the TBUT values for this subcohort had returned to baseline, but the MGS scores continued to remain significantly improved over pretreatment levels. Thus, it would appear that the period between 9 and 12 months post-treatment would be a suitable point for re-treatment, although this should be explored in a study with a larger number of subjects. However, it may be prudent to monitor TBUT in patients as they approach the 9- to 12-month post-treatment landmarks to ensure timely LTPS intervention before significant symptoms and/or meibomian gland obstruction re-manifest.

Although the total number of meibomian glands has been determined in normal subjects,<sup>19</sup> the absolute number of meibomian glands in both upper and lower eyelids that must be open, functional and producing secretions of optimal quality and quantity to support an asymptomatic state is unknown. When

considering only the meibomian glands of the lower eyelid, it has been reported that  $10.6 \pm 2.6$  open glands correlates with asymptomatic, healthy eyes,<sup>20</sup> whereas symptomatic states were observed when only  $6.25 \pm 0.35$  glands of the lower eyelid yielded liquid secretions.<sup>18</sup> Although the methods used in those studies do not allow a direct comparison with the data reported herein, the present study is consistent with the concept presented in these earlier reports that only a subset of meibomian glands need to be clinically expressible in order to achieve a relatively asymptomatic condition.

The tear film, eyelids, ocular surface and ocular adnexa form a complex system that, under optimal conditions, is adaptable enough to respond to both environmental/external challenges (pollution, decreased humidity, allergic insult, contact lens wear, air turbulence) as well as physiological changes (hormones, aging, inflammation, MGD, lacrimal gland compromise, systemic medications, incomplete blink). The design of the present study, however, does not allow an assessment of the relative influence of each of the individual anatomical and physiological tear film contributors to a dynamic, balanced system. Nevertheless, it is interesting to speculate as to the possible mechanisms that allow for such long-term sustained improvement in dry eye signs and symptoms after a single 12-min LTPS treatment. It is conceivable that the removal of the physical obstruction in the meibomian glands via LTPS treatment is more complete than manual expression or warm compress therapy, and that this degree of 'emptying' of the glands is a signal that allows a 'reset' of the checks and balances that normally operate in healthy meibomian glands. A consequence of this reset would be the renewed production of tear film-appropriate lipids in the meibomian glands, the adequate expression of the gland contents through the usual blink mechanism, the re-establishment of an adequate lipid layer, renewed protection of the ocular surface from the effects of excessive evaporation of the tear film and concomitant relief of dry eye symptoms. However, in the absence of a better understanding of the underlying pathogenesis of MGD, the mechanism whereby LTPS treatment restores physiological function and lipogenesis in particular remains largely conjecture at this point.

The primary focus of the present study was the restoration of meibomian gland function, as this parameter appears compromised in the majority of dry eye patients.<sup>9</sup> Comorbidities that also contribute to dry eye symptoms, such as aqueous deficiency (keratoconjunctivitis sicca), were not evaluated, as lacrimal-based dysfunction is not a target of Lipi-Flow technology. Nevertheless, the ability of a single, non-pharmacological LTPS treatment to essentially eliminate the meibomian gland variable

from the dry eye equation may allow future studies to dissect out the relative contribution of lacrimal gland dysfunction in those patients with underlying comorbidities and customize more effective intervention therapies.

The present study demonstrates that the improvement in the MGS score (number of meibomian glands secreting and the quality of their secretions) following a single LTPS treatment remains evident at the 1-year post-treatment landmark. Additionally, symptomatic relief continues to be significant over baseline values. These results reaffirm the value of a single LTPS treatment as a highly efficacious long-acting intervention for dry eye disease associated with MGD.

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