

A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction (MGD)

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Purpose: To evaluate the safety and effectiveness of the LipiFlow System compared to the iHeat Warm Compress (WC) for adults with meibomian gland dysfunction (MGD).

Methods: This was a non-significant risk, prospective, open-label, randomized, crossover multicenter clinical trial. One hundred thirty-nine subjects were randomized between LipiFlow (n=69) and WC control (n=70). Subjects in the LipiFlow group received a 12-minute LipiFlow treatment and were reexamined at 1 day, 2 weeks and 4 weeks. Control subjects received a 5-minute iHeat treatment with instructions to perform the same treatment daily for 2 weeks. At 2 weeks, they crossed over (LipiFlow Crossover) and received the LipiFlow treatment. Effectiveness parameters: meibomian gland (MG) assessment, tear break-up time (TBUT) and dry eye symptoms. Safety parameters: adverse events, ocular health exam, ocular surface staining, intraocular pressure, visual acuity and discomfort.

Results: LipiFlow resulted in significant improvement ($P < 0.05$) in MG secretion at 2 and 4 weeks (mean \pm standard deviation at baseline = 6.3 ± 3.5 ; 2 weeks = 14.3 ± 8.7 ; 4 weeks = 16.7 ± 8.7); and TBUT at 2 and 4 weeks: (at baseline = 5.5 ± 2.9 ; 2 weeks = 6.9 ± 5.0 ; 4 weeks = 7.4 ± 5.5). There was no significant change in MG secretion or TBUT in the control group. LipiFlow resulted in a greater significant reduction in dry eye symptoms than the iHeat WC. The crossover group demonstrated similar significant improvement 2 weeks post-treatment with the LipiFlow. There was no significant difference between groups in the incidence of non-serious, device-related adverse events.

Conclusion: The LipiFlow System was significantly more effective than iHeat WC. These results support its safety and effectiveness in the treatment of MGD and dry eye symptoms.

Key Words: Meibomian gland dysfunction, Non-obvious meibomian gland dysfunction (NOMGD), Dry eye, LipiFlow

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Meibomian gland dysfunction (MGD) is now recognized as not only a major cause of dry eye,^{1,2} but possibly, the leading cause.³ The prevailing philosophy in the mid 1990s⁴ was that aqueous deficiency explained the majority of dry eye symptoms, but an evidence-based approach to the study of dry eye has steadily shifted our focus toward MGD. This paradigm shift with respect to the etiology of dry eye is now affecting how we examine and treat patients who are at risk of manifesting or are already living with dry eye syndrome.^{5–7} Although the classical view of MGD emphasized meibomian gland infection and/or frank inflammation of the posterior eyelid margin, recent evidence strongly suggests that MGD frequently occurs in the absence of overt inflammation and infection.^{2,8} Thus, non-obvious MGD (NOMGD) is both common and frequently overlooked.⁹

Whether obvious or non-obvious, the large majority of MGD involves obstruction of the glands,¹ and there is growing support for the concept that clearance of obstruction is vital to the successful treatment of obstructive MGD.^{6–12} This suggests that treatments aimed at controlling lid margin and ocular surface inflammation and/or infection alone, without clearing the obstruction, are unlikely to be sufficient.

Current methods to relieve meibomian gland obstruction involve heat in the form of warm compresses, heated pad or goggle,^{13–16} self-administered lid massage, and/or more aggressive, practitioner-administered manual expression.^{17–19} However, warm compresses and self-administered lid massage are frequently ineffective, and manual expression by a practitioner can be very painful for the patient.²⁰

There are no conclusive studies describing and supporting an optimal warm compress therapy regime to maximally relieve meibomian gland obstruction for upper and lower eyelids.²¹ Also warm compress therapy can be both time-consuming and labor intensive,^{22,23} which can only be partially mitigated by commercialized heating pads and goggles.

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Despite the limitations of conventional methods of eyelid heating, there is evidence to show that warm compresses or various forms of heated goggles result in measurable improvements in one or more of the following: lipid layer thickness,^{13,18} meibomian gland expressibility,^{2,16,18} and dry eye symptoms.^{13,18}

These conventional forms of eyelid heating apply heat to the outer surface of the eyelid; therefore, the heat must diffuse through the layers of the eyelid skin, muscle, and the insulating tarsal plate prior to reaching the meibomian glands and their contents. A further thermal challenge is presented by the dense anterior lid vascular supply, which helps stabilize the temperature of the eyelid tissue as a function of the vasculature system in the body,^{24,25} and therefore, transports a significant portion of the applied heat away from the ocular surface.

This raises the question of what is a sufficient temperature when attempting to melt the contents of the meibomian glands. Reported melting temperatures of normal meibomian secretions vary significantly with the majority of reports ranging from 32°C to 40°C; and severely obstructed meibomian glands can have considerably higher melting points.²⁶ Warm compresses have been shown to heat the inner lid surface to a maximum of 40°C under very controlled circumstances, provided the compress is reheated and replaced every 2 minutes.²³ Thus, even if the at-home therapy was performed optimally, 40°C may not be adequate to relieve the meibomian gland obstruction depending on the severity of the obstruction. While higher temperatures are needed to alleviate significant obstruction, the physical properties of the eyelid and the tissues through which the heat must travel limit the maximum temperature that can be achieved at the meibomian glands, when applying heat to the outer eyelid.

TearScience (Morrisville, NC), has developed an innovative, in-office treatment to address the limitations of current therapeutic options to relieve obstruction of the meibomian glands and to safely administer therapeutic levels of heat and pressure. The LipiFlow System allows heat to be applied to the palpebral surfaces of the upper and lower eyelids directly over the meibomian glands, while simultaneously applying graded pulsatile pressure to the outer eyelid surfaces, thereby expressing the meibomian glands during heating.^{6,7,12} The goal of this study was to compare the clinical utility, safety and effectiveness of the LipiFlow to the standardized warm compresses, the iHeat portable Warm Compress System (Advanced Vision Research, Woburn, MA), for the treatment of obstructive MGD.

MATERIALS AND METHODS

This prospective, open-label, randomized, multicenter clinical trial was conducted in compliance with U.S. Code of Federal Regulations (CFR): 21 CFR Parts 50, 54, 56 and 812. This study was performed under the approval of an Institutional Review Board as a non-significant risk investigational device study, and all tenets of the Declaration of Helsinki for the protection of human subjects in medical research were strictly observed. Between March 4, 2009, and May 14, 2009, a total of 139 subjects (278 eyes) were enrolled at 9 sites. Inclusion criteria were subjects who: were at least 18 years of age; were willing to comply with the study

procedures and follow-up schedule; reported dry eye symptoms within 3 months of the baseline examination with a Standard Patient Evaluation for Eye Dryness (SPEED) score ≥ 6 at the baseline visit; had evidence of meibomian gland obstruction (based on a total meibomian gland secretion score of ≤ 12 for 15 glands of the lower lid) and completed the informed consent process.

Prior to the baseline visit, subjects were required to discontinue use of systemic antihistamines or isotretinoin (Accutane) for at least 1 month, cyclosporine-A (Restasis) for at least 2 months, and other dry eye or MGD related medication (e.g., antibiotics, non-steroidal and anti-inflammatory drugs, and corticosteroids) for at least 2 weeks and to maintain abstinence throughout the duration of study. (Ocular lubricants and nutritional supplements were not restricted).

Subjects were excluded if there was evidence of co-existing ocular conditions potentially posing an increased risk of procedure-related injury, (e.g. active ocular infection or inflammation in either eye); ocular surgery or trauma within 3 months of the baseline examination; ocular surface abnormality potentially compromising corneal integrity in either eye; eyelid abnormalities affecting lid function in either eye; systemic disease resulting in dry eye; and an unwillingness to abstain from systemic medications known to cause dryness for the study duration. Subjects were also excluded for co-existing conditions that could interfere with the assessment of safety and effectiveness of the treatment, (eg, macular disease; women who were pregnant, nursing or not using adequate birth control measures; etc.).

Study Design

A total of 69 subjects (138 eyes) were randomized to the LipiFlow group and received a one-time, 12-minute in-office treatment with LipiFlow. Subjects were followed at 1 day, 2 weeks and 4 weeks after initial treatment. A total of 70 subjects (140 eyes) were randomized to the Warm Compress control group and received the initial 5-minute therapy per the iHeat labeling at the treatment visit. Following 2 weeks of daily at-home use of the warm compress therapy, the subjects stopped the therapy and 68 subjects (136 eyes) received a one-time, 12-minute LipiFlow crossover treatment. Control subjects who became crossover LipiFlow subjects were followed at 1 day after the 2-week visit and at 4 weeks, which represented 1 day and 2 weeks after receiving crossover LipiFlow treatment (Figure 1). Investigators and subjects were masked as to the random treatment assignment until the treatment visit. Masking after treatment was not feasible due to the nature of the different device procedures.

Study Parameters

The primary outcome measures for effectiveness were meibomian gland assessment and tear break-up. The secondary outcome measure was dry eye symptoms.

Meibomian gland assessment was evaluated using a handheld instrument, Meibomian Gland Evaluator, along the eyelid margin to ensure measurement consistency.⁵ A total of 15 glands were evaluated along the lower eyelid margin, consisting of 5 glands located in each of the temporal, central

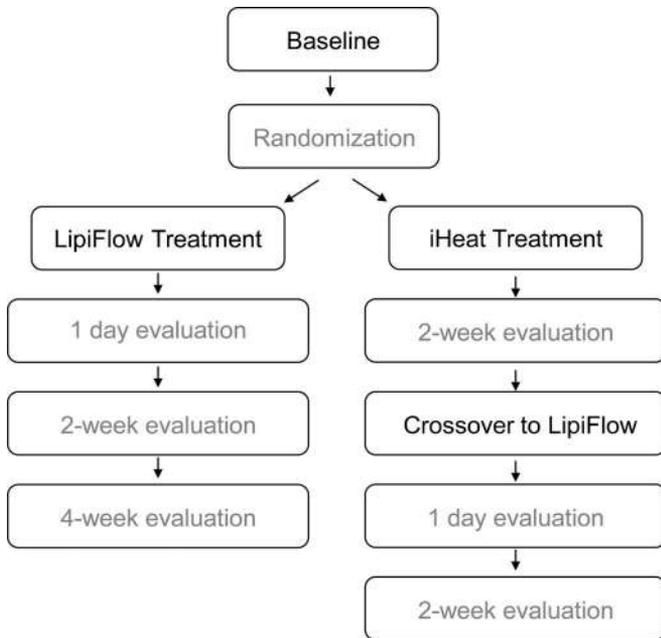


FIGURE 1. The study flow chart to illustrate the order of events

and nasal regions, as shown in Figure 2. For each of the 15 glands, expressed secretion characteristics were graded on a scale of 3 (clear liquid secretion), 2 (cloudy liquid secretion), 1 (inspissated/toothpaste consistency), and 0 (no secretion). For data analysis, 3 meibomian gland metrics were calculated: the total meibomian gland secretion score (sum of the grades for all 15 glands with a range from 0 to 45); the number of glands secreting any liquid (clear or cloudy liquid with a grade of 2 or 3) of the 15 glands assessed; and the number of glands yielding the optimal clear liquid secretion (clear liquid with a grade of 3) of the 15 glands assessed.

Tear break-up time was performed with the DET test strips (Amcon Laboratories, St. Louis, MO) using Dry Eye Test (DET) method.²⁷ The break-up time was recorded with a stopwatch and an average of 3 measurements was calculated for data analysis.

Dry eye symptoms were assessed using both the SPEED²⁸ and Ocular Surface Disease Index (OSDI)²⁹ questionnaires. The SPEED questionnaire assessed the frequency and severity of dry eye symptoms. The OSDI questionnaire assessed the subject’s frequency of dry eye symptoms and problems with

their eyes under certain tasks of daily living and environmental conditions over the previous week on a scale from 0 (none of the time) to 4 (all of the time).

For safety, the primary outcome measure was a comparison of the incidence of device-related adverse events, and secondary outcome measures were the evaluation of discomfort/pain during and after treatment and change in ocular surface (corneal and conjunctival) staining, intraocular pressure (IOP), and best spectacle-corrected visual acuity (BSCVA) with high-contrast Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart using the ETDRS-Fast method³⁰ under standard illumination.

Corneal and conjunctival staining were evaluated under a slit-lamp biomicroscope, 90 seconds after instillation of either fluorescein dye (corneal staining) or lissamine green (conjunctival staining) using a standard strip method.³¹ Based on the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye,⁴ corneal staining was graded on a scale of 0 (none) - 3 (severe) with a total corneal staining grade range from 0 to 15; and conjunctival staining was graded on a scale of 0 (none) - 3 (severe) and ranged from 0 to 18.

A subjective discomfort/pain scale⁷ was used during, immediately after treatment, and post-treatment at day 1. Discomfort was recorded on a scale from 0 to 10, as follows: 0, no discomfort; 1–2, slight or transient awareness of pressure without pain; 3–4, moderate discomfort with minimal pain; 5–6, moderate pain; 7–8, severe pain; and 9–10, intolerable pain.

The LipiFlow System

The LipiFlow System is an innovative medical device designed to safely heat the palpebral surfaces of both the upper and lower eyelids, while simultaneously applying graded pulsatile pressure to the outer eyelid surfaces. The device massages the outer eyelids from the base of the meibomian glands in the direction of the gland orifices, thereby expressing the meibomian glands during heating. The LipiFlow System is composed of 2 primary components, an ocular component (The Disposable) and a Handheld Control System. The Disposable has 2 parts, a Lid Warmer and an Eyecup.

The Lid Warmer resembles a large oval scleral lens designed to rest on the bulbar conjunctiva and vault the cornea. The concave side of the Lid Warmer is comprised of an insulating material, which, in addition to the air gap created by the corneal vault, shields the cornea and ocular surface from direct exposure to the heat. The convex side of

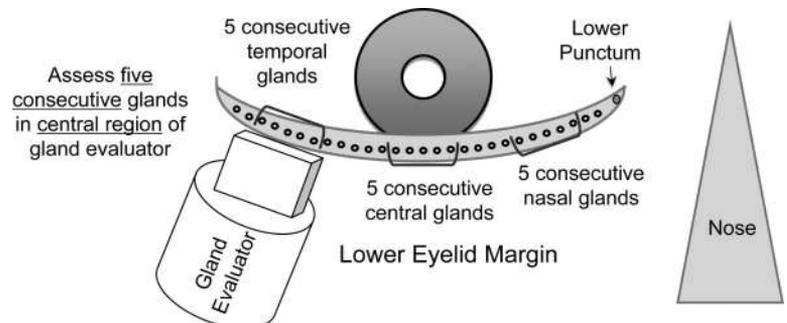


FIGURE 2. Schematic to illustrate the meibomian gland diagnostic evaluation of the lower eyelid.

the Lid Warmer contains an imbedded precision heater to regulate the temperature applied to the inner surface of the eyelids, providing a heated surface with a nominal average temperature at the palpebral conjunctiva between 41°C and 43°C. The Eyecup presents an inflatable air bladder to the external lid surfaces and rests over the closed eyelids. During treatment, the air bladder inflates, compressing the eyelids between the heated Lid Warmer and the bladder (Figures 3, 4). Prior to insertion, 2 drops of a commercially available topical anesthetic were administered to the treatment eye. The Disposable was inserted, as one would a scleral lens or surgical corneal shield, and the subject was instructed to close his/her eyes to ensure proper device position on the eyelids before treatment was initiated.

Warm Compress Control

The iHeat portable Warm Compress is a commercially available, over-the-counter, standardized chemical pack intended to heat the external lids and surrounding tissue. It consists of a disposable warming unit for each eye that is activated by the consumer and placed in the provided eye mask, which is worn over the eyes for 5 minutes as per the manufacturer's instructions. All Control subjects experienced their first iHeat treatment in the office to ensure that they fully understood the directions. They were then instructed to use the warm compress system for at least 10 days (the mean \pm standard deviation number of days of warm compress use was 14.4 ± 1.6 days). To evaluate compliance with the iHeat the subjects were required to fill out a daily log documenting their use of the iHeat and to return all used and unused heat packs.

Statistical Analysis

Statistical analysis was performed using SAS software (Cary, NC). Analysis included: paired two-tailed t-test for comparison of baseline and post-treatment outcomes for each treatment group; two sample two-tailed t-tests for comparison

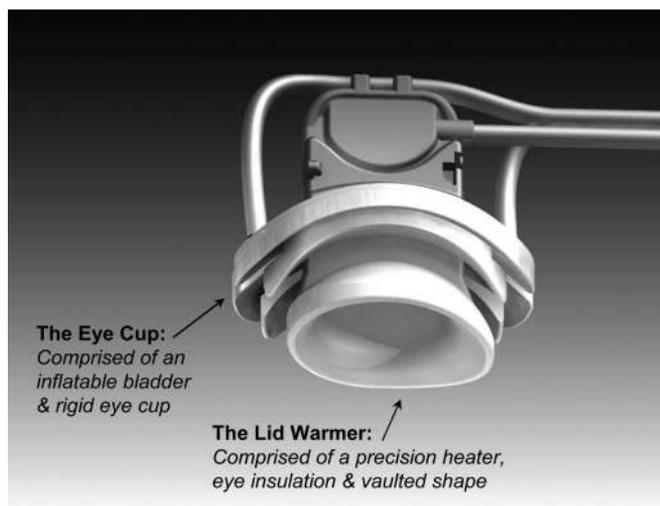


FIGURE 3. The LipiFlow Disposable unit showing the rigid Eyecup and the insulated Lid Warmer used to manually express and simultaneously heat the meibomian glands.

of the mean change from baseline to 2 weeks between LipiFlow and Control groups; and Fischer Exact Test for comparison of the incidence of device-related adverse events between LipiFlow and Control groups. For the primary and secondary outcome measures, a statistically significant difference was based on an $\alpha=0.05$ (P -value < 0.05). All enrolled intent-to-treat subjects ($n=139$ subjects; 278 eyes) were analyzed for safety and all eligible per-protocol treated subjects ($n=133$ subjects; 266 eyes) were analyzed for effectiveness. Since protocol deviations such as concomitant use of other dry eye or MGD therapy may enhance effectiveness outcomes, the per-protocol analysis was more appropriate to assess the effectiveness of the LipiFlow treatment alone. There were no protocol deviations related to non-compliance with the Control warm compress therapy. In addition, the statistically significant trends observed for effectiveness outcomes in the per-protocol population were also observed for the intent-to-treat population.

Analysis of effectiveness parameters was based on the change from baseline to 2 weeks for each group with a comparison of the change between the LipiFlow and Warm Compress Control groups. In addition, the duration of effectiveness for the LipiFlow was evaluated at 4 weeks based on the change from baseline.

RESULTS

Comparison of the LipiFlow to Warm Compress Efficacy

Meibomian Gland Assessment & Tear Break-up Time (Primary Efficacy Measures)

The LipiFlow group demonstrated a statistically significant mean increase from baseline to 2 weeks for all the 3 metrics of meibomian gland secretion characteristics (total meibomian gland score, number of glands secreting any liquid, and number of glands yielding clear liquid secretion) as well as tear break-up time (Table 1). In contrast, the Warm Compress Control group did not show a statistically significant mean change from baseline to 2 weeks for either meibomian gland assessment or tear break-up time.

Comparison of the change from baseline to 2 weeks between the 2 groups demonstrated that the LipiFlow group had a statistically significant greater mean improvement in both the meibomian gland secretion characteristics and tear break-up time as compared to the Warm Compress Control group (Table 2).

Dry Eye Symptoms (Secondary Efficacy Measure)

Both the LipiFlow and warm compress control groups had a statistically significant mean decrease from baseline to 2 weeks in the total SPEED and OSDI scores, reflecting a reduction in dry eye symptom frequency and severity in both groups (Table 1). However, the LipiFlow group had a statistically significant greater mean decrease in total SPEED and OSDI scores between baseline and 2 weeks than the warm compress control group (Table 2).

An overall improvement in dry eye symptoms was reported by 76% of the LipiFlow group vs. 56% of the warm compress control group at 2 weeks. An improvement of 50%

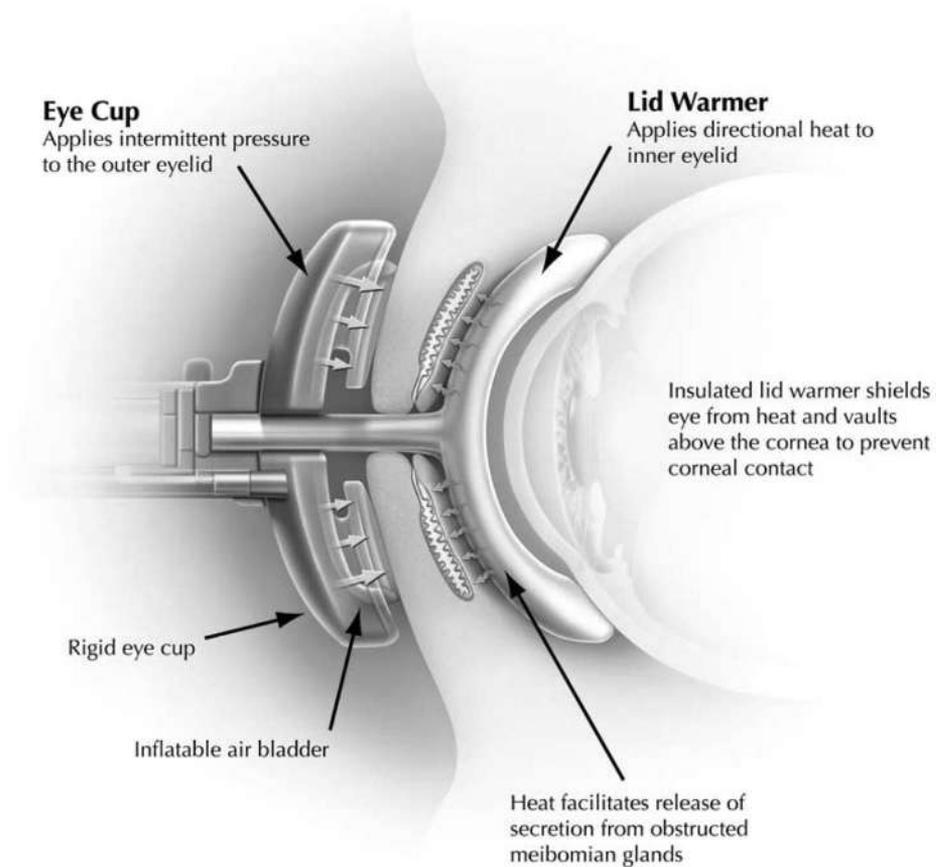


FIGURE 4. During treatment, the air bladder inflates; the eyelids are compressed between the heated Lid Warmer and the bladder. The bladder inflates and deflates so as to massage the eyelids from the terminal end of the meibomian gland in the direction of the meibomian gland orifices.

or greater was reported in 43% of the LipiFlow group vs. only 11% of the warm compress control group.

LipiFlow Efficacy at 4 Weeks and 2 Weeks After Crossover

Meibomian Gland Assessment & Tear Break-up Time (Primary Efficacy Measures)

The LipiFlow group (non-crossover arm) demonstrated a statistically significant mean increase from baseline to 4 weeks for all 3 metrics of meibomian gland assessment and tear break-up time, indicating sustained effectiveness (Table 1). The control group, which did not show a statistically significant improvement in any of the meibomian gland assessment measures or tear break-up time, did demonstrate a statistically significant mean increase in these metrics after crossing over to the LipiFlow treatment (Table 1).

Dry Eye Symptoms (Secondary Efficacy Measure)

The LipiFlow group (non-crossover arm) continued to show reduction of dry eye symptoms over the 4-week study duration with a statistically significant mean decrease from baseline to 4 weeks in the total SPEED and OSDI scores (Table 1). The Crossover LipiFlow group demonstrated a reduction in symptoms after the warm compress treatment and then a further statistically significant mean reduction in symp-

toms on both SPEED and OSDI scores after the crossover LipiFlow treatment (Table 1).

Comparison of LipiFlow to Warm Compress Safety

Incidence of Device-Related Adverse Events (Primary Safety Measure)

There were no unanticipated or serious device-related adverse events reported. Device-related, non-serious adverse events were reported for 3 eyes of the LipiFlow group with moderate eyelid pain, 1 eye of the LipiFlow group with moderate conjunctival vascular injection, and 2 eyes of the Warm Compress Control group with moderate ocular burning symptom. There was no statistically significant difference between groups in the incidence of device-related adverse events ($P = 0.45$; Fischer Exact Test). All of these adverse events resolved during the 4-week study without sequelae or the need for medical treatment. In addition, there were no device-related adverse events in the crossover LipiFlow group.

Additional Safety Measures (Discomfort/Pain, Ocular Surface Staining, IOP, and BSCVA)

The mean discomfort score during LipiFlow treatment was 1.4 on a scale of 0 to 10 and within the category of

TABLE 1. Summary of Effectiveness by Treatment Group – Per-Protocol Population

Effectiveness Parameter	LipiFlow					Warm Compress Control			Crossover LipiFlow	
	Baseline (n=130)	2 weeks (n=130)	Change baseline to 2 weeks	4 weeks (n=128)	Change baseline to 4 weeks	Baseline (n=136)	2 weeks	Change baseline to 2 weeks	4 weeks (n=132)	Change 2 weeks to 4 weeks
	mean (SD)	mean (SD)	P-value*	mean (SD)	P-value*	mean (SD)	mean (SD)	P-value*	mean (SD)	P-value*
Meibomian Gland Assessment							(n = 136 eyes)			
Total Meibomian Gland Score (0 to 45)	6.3 (3.5)	14.3 (8.7)	<0.0001	16.7 (8.7)	<0.0001	5.6 (3.9)	6.1 (5.6)	0.3214	11.7 (7.3)	<0.0001
# Glands Secreting Any Liquid (0 to 15)	1.9 (1.6)	4.9 (3.6)	<0.0001	5.8 (3.5)	<0.0001	1.9 (1.8)	2.1 (2.3)	0.315	4.2 (3.3)	<0.0001
# Glands Yielding Clear Liquid (0 to 15)	0.6 (0.9)	2.0 (2.9)	<0.0001	2.6 (3.6)	<0.0001	0.4 (0.8)	0.5 (1.1)	0.6198	1.2 (1.9)	<0.0001
Tear Break-up Time							(n = 136 eyes)			
Tear Break-up Time (0 to 20 seconds)	5.5 (2.9)	6.9 (5.0)	<0.0001	7.4 (5.5)	<0.0001	5.4 (3.5)	5.3 (3.5)	0.6492	6.3 (4.7)	0.0027
Dry Eye Symptom Questionnaire							(n = 134 eyes)			
Total SPEED Score (0 to 28)	14.3 (4.8)	8.1 (5.5)	<0.0001	7.6 (5.8)	<0.0001	14.8 (4.8)	11.2 (5.4)	<0.0001	7.9 (5.6)	<0.0001
Total OSDI Score (0 to 100)	32.0 (20.0)	17.3 (17.2)	<0.0001	16.6 (18.1)	<0.0001	34.7 (19.6)	26.9 (18.2)	<0.0001	21.0 (18.3)	0.0002

n = number of eyes analyzed, SD = Standard Deviation.

*2-tailed paired sample t-test for mean change over time for each group.

awareness of pressure without pain (scores 1 to 2). The maximum score reported for one LipiFlow eye during treatment was 6, which reduced to 4 after the physician changed the setting to Low Pressure mode during treatment (Table 3). Any discomfort reported during LipiFlow treatment resolved either immediately post-treatment or by the 1-day visit for the majority of subjects (88.4% of the LipiFlow and 83.8% of the Crossover LipiFlow group). The mean score immediately after the treatment as well as at the 1-day visit for the LipiFlow group was 0.2 with a maximum of 3 to 4.

The mean sum of corneal staining scores across 5 corneal regions was low (less than 3.0 on a scale from 0 to 15) for both groups at each visit (Table 4). No eyes in the study had a corneal epithelial defect immediately after treatment or 1-day visits. The LipiFlow group showed a minimal, but statistically significant mean increase in corneal staining of 0.8 from pre-treatment to immediately post-treatment (Table 3). However, at the 1-day visit, the mean corneal staining score for the LipiFlow group improved to slightly less than baseline indicating the staining after treatment was transient (Table 4). Additionally, in the LipiFlow group, there was a statistically

TABLE 2. Comparison of Change in Effectiveness Parameters From Baseline to 2 Weeks LipiFlow vs. Warm Compress Control

Change in Effectiveness Parameter Baseline to 2 Weeks	LipiFlow	Warm Compress Control	LipiFlow vs. Control
	Mean (SD) Change Baseline to 2 Weeks	Mean (SD) Change Baseline to 2 Weeks	P-value**
Meibomian Gland Assessment	(n = 130 eyes)	(n = 136 eyes)	
Change in Total Meibomian Gland Score	7.9 (8.6)	0.5 (5.3)	<0.0001
Change in Number of Glands Secreting Any Liquid	3.0 (3.5)	0.2 (2.5)	<0.0001
Change in Number of Glands Yielding Clear Liquid	1.4 (2.8)	0.1 (1.2)	<0.0001
Tear Break-up Time	(n = 130 eyes)	(n = 136 eyes)	
Change in Tear Break-up Time (seconds)	1.5 (4.5)	0.1 (3.7)	0.0017
Dry Eye Symptom Questionnaire	(n = 130 eyes)	(n = 134 eyes)	
Change in Dry Eye Symptoms: Total SPEED Score	-6.2 (5.6)	-3.5 (4.7)	<0.0001
Change in Dry Eye Symptoms: Total OSDI Score	-14.7 (14.4)	-8.1 (15.8)	0.0004

**2-tailed two-sample t-test for mean difference between the LipiFlow and Warm Compress Control groups.

TABLE 3. Comparison of Safety Parameters for LipiFlow vs. Warm Compress Control

Safety Parameters	LipiFlow		Warm Compress Control		LipiFlow vs. Control	Pooled LipiFlow		Pooled LipiFlow vs. Control	
	n eyes	% eyes	n eyes	% eyes	P-value†	n eyes	% eyes	P-value†	
Adverse Events	(n = 138 eyes)		(n = 140 eyes)			(n = 274 eyes)			
Device-Related Adverse Events	4	2.9%	2	1.4%	0.4455	4	1.5%	1.0	
Best Spectacle-Corrected Visual Acuity (BSCVA)	(n = 136 eyes)		(n = 140 eyes)			(n = 272 eyes)			
2-Week BSCVA ≥ 2 lines (≥ 0.20 logMAR) Worse than Baseline	2	1.5%	4	2.9%	0.6843	3	1.1%	0.2348	
	Mean (SD)		Mean (SD)		P-value**	Mean (SD)		P-value**	
Discomfort/Pain Score	(n = 138 eyes)		(n = 140 eyes)			(n = 274 eyes)			
Discomfort/Pain During Treatment	1.4	(1.4)	0.1	(0.7)	<0.0001	1.3	(1.4)	<0.0001	
Discomfort/Pain After Treatment	0.2	(0.6)	0.0	(0.2)	0.0001	0.2	(0.6)	<0.0001	
Ocular Staining (sum score)	(n = 138 eyes)		(n = 140 eyes)			(n = 274 eyes)			
Change in corneal staining pre-treat to post-treat	0.8	(2.2)	0.2	(1.3)	0.0032	0.8	(2.1)	0.0003	
Change in corneal staining Baseline to 2 Weeks	-0.4	(2.1)	0.0	(1.7)	0.0691	-0.4	(2.0)	0.0379	
Change in conjunctival staining pre-treat to post-treat	0.1	(2.7)	0.0	(1.3)	0.6486	0.2	(2.4)	0.2250	
Change in conjunctival staining Baseline to 2 Weeks	0.4	(2.0)	0.0	(2.2)	0.1071	0.3	(2.1)	0.1742	
Intraocular Pressure (IOP) (mm Hg)	(n = 138 eyes)		(n = 140 eyes)			(n = 274 eyes)			
Change in IOP pre-treat to post-treat	0.8	(2.7)	0.9	(2.3)	0.5619	0.3	(2.4)	0.0096	
Change in IOP Baseline to 2 Weeks	-0.5	(2.7)	-0.2	(2.6)	0.2921	-0.8	(2.7)	0.0251	

†Fisher Exact Test for comparison of LipiFlow vs. Warm Compress Control.

**2-tailed two-sample t-test for mean difference between the LipiFlow and Warm Compress Control groups.

significant mean decrease in corneal staining from baseline to 2 weeks and 4 weeks. In the warm compress control group, no statistically significant change in mean corneal staining was observed from pre-treatment to immediately post-treatment or from baseline to 2 weeks.

The mean sum of conjunctival staining scores across 6 conjunctival regions was also low (less than 2.0 on a scale from 0 to 18) for both groups at each visit (Table 4). While the

Warm Compress Control group did not show a statistically significant mean change in conjunctival staining from baseline to 2 weeks, the LipiFlow group had a small (0.3 to 0.4) statistically significant mean increase in conjunctival staining from baseline to 2 weeks and 4 weeks. The mean increase in staining at 2 and 4 weeks reflects a negligible change in conjunctival surface dryness or irritation from baseline. In addition, there was no statistically significant difference in the mean change in

TABLE 4. Summary of Safety for LipiFlow Group

Safety Parameter	Baseline	Pre-Treat	Post-Treat	Change	1	Change	2	Change	4 Weeks	Change
	(n = 138)	(n = 138)	(n = 138)	Pre-Treat to Post-Treat	Day (n = 138)	Baseline to 1 Day	Weeks	Baseline to 2 Weeks	(n = 138)	Baseline to 4 Weeks
	mean (SD)	mean (SD)	mean (SD)	P-value*	mean (SD)	P-value*	mean (SD)	P-value*	mean (SD)	P-value*
Ocular Staining							(n = 138 eyes)			
Corneal Staining Sum Score (0 to 15)	2.2 (2.2)	2.1 (1.9)	2.9 (2.4)	<0.0001	1.9 (2.3)	0.0834	1.9 (2.0)	0.0333	1.5 (1.7)	0.0003
Conjunctival Staining Sum Score (0 to 18)	1.3 (2.1)	1.4 (2.3)	1.5 (2.3)	0.5505	1.4 (2.6)	0.6303	1.7 (2.5)	0.016	1.6 (2.5)	0.0376
Intraocular Pressure							(n = 138 eyes)			
Intraocular Pressure (mm Hg)	13.3 (3.3)	13.5 (3.3)	14.3 (3.3)	0.0013	13.7 (2.8)	0.0406	12.8 (2.8)	0.0289	12.5 (2.9)	0.0006
BSCVA							(n = 136 eyes)			
BSCVA (logMAR)	0.00 (0.12)	-	-	-	-	-	-0.02 (0.13)	0.1411	-0.02 (0.12)	0.1119

*2-tailed paired sample t-test for mean change over time.

conjunctival staining for the LipiFlow group vs. the Warm Compress Control group from pre-treatment to immediately post-treatment or from baseline to 2 weeks after treatment (Table 3).

Both the LipiFlow and Warm Compress Control groups had a minimal (<1 mm Hg) mean increase in IOP from pre-treatment to immediately post-treatment. The LipiFlow group also had a slight mean increase in IOP from baseline at 1 day, and a mean decrease in IOP from baseline at 2 weeks and 4 weeks. As shown in Table 4, the mean changes in IOP of less than 1 mm Hg from baseline at all post-treatment visits were negligible. Furthermore, there was no statistically significant difference in the mean IOP change for the LipiFlow group vs. the Warm Compress Control group from pre-treatment to immediately post-treatment or from baseline to 2 weeks. There was no statistically significant mean change in logMAR BSCVA for the LipiFlow group from baseline to 2 weeks and 4 weeks after treatment. Similarly, the Warm Compress Control group had no statistically significant mean change in BSCVA from baseline to 2 weeks.

Changes from baseline to post-treatment slit lamp findings which did not meet the adverse event criteria were noted in less than 5% of eyes. The most common findings for the LipiFlow and Crossover LipiFlow groups were trace to mild conjunctival injection, hyperemia or redness; and trace or mild petechial hemorrhages on the eyelid or conjunctiva immediately post-treatment or at 1 day which were fully resolved by the 2-week visit without any treatment. There were no changes in the intraocular findings from baseline based on dilated retinal exam except for one case of posterior vitreous floaters, which was unrelated to device use.

DISCUSSION

The goal of this study was to compare the safety and effectiveness of standardized warm compress therapy, applied daily over a 2-week period, to that of a novel treatment, the LipiFlow, applied only once for a 12-minute in-office treatment. The study included a crossover arm, permitting control subjects to receive the LipiFlow treatment after they had completed their warm compress protocol. This allowed all enrolled subjects to receive the LipiFlow treatment while also incorporating a control against which the LipiFlow System could be compared.

For all of the objective tests performed to assess treatment effectiveness – meibomian gland secretion score, the number of glands yielding liquid secretion and tear break-up time —LipiFlow performed significantly better and showed significantly greater improvement in symptoms than the warm compress control. The Crossover LipiFlow group showed similar statistically significant effectiveness trends. The Warm Compress Control group did not show a statistically significant improvement in any of the objective effectiveness measures.

As this was an open label study, there is always the possibility that investigator bias affected the objective study outcomes. As such, we elected to perform this study at 9 different clinical sites to help dilute any potential bias generated by one particular investigator. The results of the study demonstrated fairly even results across all 9 sites further indicating no obvious investigator bias from any one site.

The subjects who only received the LipiFlow treatment were followed at 4 weeks. While this study was not intended to evaluate the long-term duration of effect, it was encouraging to see that the initial improvement in signs and symptoms was maintained throughout the 4-week study period. The trend towards further improvement in signs and symptoms at the 4-week visit compared to the 2-week visit offers a positive prognosis for future studies evaluating a longer duration. We speculate that this continued improvement may be due to restoration of function of previously blocked, dysfunctional meibomian glands. We further hypothesize that the increase in gland function improves the tear film stability, which may positively influence other objective and subjective measures of ocular surface health; in this case, tear break-up time and symptom scores.

An area of additional interest, which was not addressed in this study, is the evaluation of the functionality of the upper lid meibomian glands. This was not performed as no standardized technique has been defined for the evaluation of the upper lid meibomian glands. To obtain a clear view of the upper lid meibomian glands, eyelid eversion is usually required, but the force it exerts on the glands during lid eversion compromises any objective data gathered on gland functionality. Despite the lack of a reliable metric by which the upper lid meibomian glands can be assessed, both the upper and lower lids should be treated to achieve the most effective outcomes.

Patients with significant eyelid inflammation and infection were excluded from this study. This novel form of treatment, heating the meibomian glands from the palpebral surfaces of the upper and lower eyelids combined with simultaneous pressure to express the meibomian glands, may not be appropriate as an initial treatment for significantly inflamed or infected forms of MGD. However, in such cases, the obstructed glands could benefit from this treatment after medications to manage the inflammation and/or infection have been initiated. Patients suffering from meibomian gland obstruction who benefit from this treatment may require additional treatments, as the meibomian glands may become obstructed again over time. Duration of effect studies will be necessary to accurately predict the optimal frequency of treatment for individual patients.

It is encouraging to note that, unlike conventional physician-administered manual expression, the LipiFlow treatment did not generate pain or significant discomfort for the majority of subjects. In most cases, there was only mild discomfort experienced during treatment (score of ≤ 4 on a scale of 0 to 10); 97.1% in LipiFlow group and 99.3% in the Crossover LipiFlow group. This is in stark contrast to non-heated manual expression, which, despite topical anesthesia can be very painful²⁰ and may result in significant eyelid edema and bruising. Patients who require conventional manual expression and those who devote significant amounts of time (5 – 30 minutes daily) to warm compress therapy may find a single 12-minute treatment an attractive alternative.

CONCLUSION

—A single 12-minute treatment with the LipiFlow System provided sustained improvement in both signs and symptoms over the 4-week study.

- The safety profile of the LipiFlow System reflects a low occurrence of non-serious, transient side effects that resolve quickly and do not require medical treatment.
- This randomized controlled clinical trial demonstrated the clinical utility, safety and effectiveness of the LipiFlow System in adult patients with MGD and dry eye symptoms.

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