

# A Comparison of TearCare and Lipiflow Systems in Reducing Dry Eye Disease Symptoms Associated with Meibomian Gland Disease

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**Purpose:** To compare TearCare and Lipiflow systems in the ability to reduce the symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD).

**Methods:** In this multicenter, masked, randomized-controlled trial, 235 subjects received a single TearCare treatment (n = 115) or a single LipiFlow treatment (n = 120) and were followed for 1-month post-treatment. DED symptoms were assessed using the Ocular Surface Disease Index (OSDI), Symptom Assessment in Dry Eye (SANDE), and Eye Dryness (ED) questionnaires at baseline and at 1 month. Post-hoc subgroup analysis was conducted on subjects with less severe and more severe gland obstruction determined by baseline meibomian gland secretion score (MGSS).

**Results:** TearCare system significantly improved total OSDI, SANDE, and ED scores from baseline ( $p < 0.0001$ ) at 1-month follow-up. Subjects with more severe disease (MGSS  $< 7$ ) achieved statistically greater reduction with TearCare compared to LipiFlow in total OSDI score ( $30.4 \pm 2.53$  and  $21.9 \pm 2.37$ , respectively,  $p_{\text{ANCOVA}} = 0.0160$ ), OSDI Section B score for quality of vision ( $5.1 \pm 0.48$  and  $3.6 \pm 0.45$ , respectively,  $p_{\text{ANCOVA}} = 0.0206$ ), and SANDE frequency score ( $51.9 \pm 3.70$  and  $41.5 \pm 3.45$ , respectively,  $p_{\text{ANCOVA}} = 0.0455$ ).

**Conclusion:** TearCare provides significant DED symptom relief at 1 month after a single treatment. Outcomes were consistent in OSDI, SANDE, and ED assessments. In subjects with more severe gland dysfunction, TearCare performed significantly better than LipiFlow in improving quality of vision and overall DED symptom frequency determined by OSDI and SANDE.

**Clinical Trial Registration Number:** NCT03857919.

**Keywords:** dry eye disease, meibomian gland deficiency, TearCare procedure

## Introduction

Dry eye disease (DED) is a prevalent chronic eye condition affecting between 5% and 34% of the population worldwide, and approximately 1 million to 4 million Americans between 65 and 84 years of age.<sup>1,2</sup> This multifactorial disease has considerable socio-economic implications, including daily activities, visual function, social and physical functioning, workplace productivity, and quality of life.<sup>3</sup>

DED is defined as

a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.<sup>4</sup>

Based on etiology, DED can be classified as aqueous tear deficiency, evaporative tear deficiency, or a combination of both. According to a report by the Tear Film & Ocular Surface Society Dry Eye Workshop in 2017, evaporative DED is more common than aqueous-deficiency DED.<sup>4</sup> Evaporative DED results from excessive loss of water due to

exposed ocular surface despite normal lacrimal secretion. Consequently, a vicious cycle is generated, in which tear hyperosmolarity develops and activates inflammation response that contributes to tear film instability, further exacerbating tear hyperosmolarity. Etiologies of evaporative DED include meibomian gland deficiency (MGD), poor lid dynamic, low blink rate, systemic retinoids use, preservatives use, contact lens, vitamin A deficiency, etc. The most common cause for evaporative DED is MGD which causes disruption of the tear lipid layers.<sup>5</sup> Chronic glandular inflammation, meibum thickening, gland channel terminal duct obstruction, and glandular atrophy associated with MGD lead to altered meibomian gland secretions and tear film instability. A treatment approach for MGD by restoring meibomian gland function and natural flow of meibum has potential therapeutic relief for DED signs and symptoms.<sup>6</sup>

Three commonly used products for DED are available in the United States, targeting the inflammatory aspects of the disease: Restasis<sup>®</sup>, Xiidra<sup>®</sup>, CEQUA<sup>™</sup>. However, these currently approved pharmacologic treatments for DED are associated with delayed onset of action for both DED sign and symptom improvements. Clinical experiences reported at least 6 weeks for improved signs and 12 weeks for symptom relief with Xiidra<sup>®</sup>, 21 weeks for improved signs with Restasis<sup>®</sup>, and 12 weeks for improved signs with CEQUA<sup>™</sup>.<sup>7–9</sup> It is evident that data for DED symptom improvements with current therapies are limited, and there exists a therapeutic need for faster onset treatments.

Meanwhile, MGD treatment mainly begins from eyelid warming, eyelid massaging, and progresses to the uses of topical lubricants, topical and systemic antibiotics with anti-inflammatory properties, and topical steroids. A number of devices have been developed for eyelid warming to optimize efficacy and compliance with faster onset of action such as LipiFlow and TearCare systems. The LipiFlow Thermal Pulsation System (Johnson & Johnson Vision, Milpitas, CA, USA), indicated for adult patients with MGD, can safely heat the palpebral surfaces of the upper and lower eyelids while applying graded pulsatile pressure to the outer surface. An open label, randomized, crossover study in 139 subjects demonstrated that a single 12-minute treatment with LipiFlow maintained improvement in both signs and symptoms over the 4-week study.<sup>10</sup> The TearCare System (Sight Sciences, Menlo Park, CA, USA), a class II exempt device listed with the FDA for the application of warm compress to eyelids, delivers controlled, precise heat to the tarsal plates and underlying meibomian glands for 15 minutes followed by manual mechanical meibomian gland expression. The TearCare system allows subjects to blink naturally thanks to the flexible SmartLid devices applied to the upper and lower eyelid surfaces. The SmartHub component of the TearCare system provided adjustable temperature ranging from 41 to 45 °C for subject comfort.

Previous study in 2017 on 24 subjects demonstrated that the TearCare System significantly improved tear film break-up time (TFBUT), meibomian secretion, corneal and conjunctival staining scores, and dry eye symptom questionnaires at 1-month follow-up and maintained these outcomes out to 6 months<sup>11</sup> and 12 months.<sup>12</sup> The outcomes were further validated in multicenter studies concluded in 2018<sup>13</sup> and 2019.<sup>14</sup> This report aims to highlight DED symptom improvement efficacy results of TearCare from an unpublished clinical report of OLYMPIA study on 235 subjects and its post-hoc subgroup analysis.

## Materials and Methods

### Study Design

OLYMPIA study was a randomized, single-masked, multicenter, non-inferiority, post-market study to evaluate the safety and effectiveness of a single TearCare treatment compared to a single LipiFlow treatment for improving signs and symptoms of DED associated with MGD. The study was approved by the institutional review board (Aspire IRB) and conducted in accordance with the Declaration of Helsinki. After explanation of the study was given, subjects with DED who were  $\geq 22$  years of age and provided informed consent were randomized 1:1 to receive one in-office treatment of either the TearCare system or LipiFlow Thermal Pulsation on study day 0. Subjects could not be masked due to apparent treatment design. Subjects must have Ocular Surface Disease Index (OSDI) score of 23–79, TFBUT of  $\leq 7$  seconds in both eyes, and best corrected visual acuity of 20/100 or better in both eyes. At least 15 glands in each lower eyelid should be expressible, and total Meibomian Gland Secretion Score (MGSS) must be  $\leq 12$  in each eye.

Study staff performing endpoint assessments were masked to the subject's treatment arm. The study comprised 4 visits: Baseline, Treatment (if not at Baseline Visit), Day 1, Week 2, and Month 1. Within the 1-month follow-up, subjects refrained from using any dry eye drops, lubricants, or other type of dry eye treatment (eg warm compresses, prescription medication, etc.). If they required "rescue therapy" for relieve symptoms, they could use the same type of drops or lubricants they were using prior to the study and recorded any use in the Dry Eye Lubricant/Drop Log.

In this study, DED symptoms were assessed as secondary endpoints using the Eye Dryness (ED) score, mean change from baseline in OSDI score, and mean change from baseline in Symptom Assessment in Dry Eye (SANDE) scores.

## Symptom Endpoint Assessments

### OSDI

The OSDI questionnaire is a valid and reliable instrument for measuring dry eye symptoms (normal, mild to moderate, and severe) and its effect on vision-related functions. The investigator asked subjects 12 questions which were categorized into three subsections: Section A (ocular symptoms), Section B (vision-related functions), and Section C (environmental triggers). The OSDI was assessed on a scale of 0 to 100 with higher score representing greater disability. The 5-unit scale for responses to the OSDI was given by the following: 0 = None of the time, 1 = Some of the time, 2 = Half of the time, 3 = Most of the time, and 4 = All of the time. The total OSDI score was calculated by the following:

$$\text{OSDI score} = \frac{(\text{Sum of Scores}) \times 25}{\text{\# of Questions Answered}}$$

Note that the number of questions answered in the denominator should exclude those questions with a response of "N/A."

Based on the calculated OSDI score, the severity of the subject's dry eye symptoms was classified as Normal (0–12), Mild (13–22), Moderate (23–32), and Severe (33 or higher).

### SANDE

The SANDE questionnaire is an instrument containing two questions to assess frequency and severity of DED symptoms. It is useful to detect changes in symptoms over time. Each item was assessed on a 100 mm Visual Analog Scale (VAS) ranging from Never to All the time for frequency assessment and from Very comfortable to Very severe for severity assessment. Subjects were asked to respond by placing a vertical line across the horizontal line of the VAS. SANDE Score (ranging from 0 to 100) is the distance (in mm) between the left end of the scale and the subject's response.

### Eye Dryness Score

The Eye Dryness (ED) Score measures the subject's level of discomfort related to eye dryness ranging from No Discomfort to Maximal Discomfort. Subjects were asked to respond by placing a vertical line across the horizontal line of the VAS. The ED Score (ranging from 0 to 100) is the distance (in mm) between the left end of the scale and the subject's response.

### Meibomian Gland Score

The Meibomian Gland Secretion Score (MGSS) is an assessment of the quality of the secretion produced by the meibomian glands in the lower eyelids. This assessment was performed by the masked assessor.

Quality of secretions of 5 central glands in the lateral, central and temporal thirds of the lower eyelids; a total of 15 glands per eye was graded using the method described by Korb and Blackie.<sup>15</sup> The part of the instrument's contact surface was placed onto the skin immediately inferior to the eyelashes of the lower eyelid so that the long dimension is parallel to the eyelid margin. Once full contact was achieved between the instrument and the skin immediately below the lash line of the lower lid, the shaft of the instrument was rotated downward approximately 15 to 45 degrees. Then, the shaft was depressed midway (~3 mm) and the lower eyelid margin was rolled slightly outward. The instrument was held in place over each third of the lid for a minimum of 10 and a maximum of 15 seconds while grading the quality of secretion of the 5 glands in the center of the instrument (15 glands total per eye) as per the following scale described by Lane et al:<sup>16</sup>

- 0= nothing
- 1= toothpaste
- 2= cloudy
- 3= clear

From this assessment the total MGSS was computed as: Sum of the grade (0–3) for each of the 15 glands. Range for this score is 0–45.

## Statistical Analyses

The analysis of symptoms assessments was conducted on all randomized subjects and two post-hoc subgroups stratified by median baseline MGSS reflecting the severity of meibum and meibomian gland dysfunction at baseline: one group with MGSS above the median ( $\geq 7$ ) representing less severe dysfunction and one with MGSS below the median ( $< 7$ ) indicating more severe dysfunction. The DED symptom endpoints were measured on per-subject basis and analyzed via a paired *t*-test and baseline-adjusted analysis of covariance (ANCOVA) to evaluate change from baseline to 1-month post-treatment and difference between two treatment groups.

## Results

### Baseline Characteristics

This study was conducted at 10 multispecialty eye care facilities across the United States between March 2019 and February 2020. The analysis population comprised 235 subjects with 115 subjects in the TearCare group and 120 subjects in the LipiFlow group. The distribution of gender and race was similar across treatment groups. There were no distinguished differences between the study groups as well as the subgroups stratified by MGSS (Table 1). For DED baseline symptoms, the TearCare group and LipiFlow group had similar baseline mean OSDI score ( $51.7 \pm 14.79$  and  $51.7 \pm 15.27$ , respectively), mean total SANDE score ( $70.6 \pm 16.78$  and  $77.2 \pm 15.82$ , respectively), and mean ED score ( $69.9 \pm 20.15$  and  $71.9 \pm 18.48$ , respectively).

The subgroup population including subjects with more severe disease determined by baseline MGSS  $< 7$  comprised 56 subjects in the TearCare group and 65 subjects in the LipiFlow group. The subgroup population of subjects with less severe dry eye disease (baseline MGSS  $\geq 7$ ) included 59 subjects in the TearCare group and 55 subjects in the LipiFlow group.

**Table 1** Demographics of TearCare and LipiFlow Groups

	TearCare			LipiFlow		
Groups	All	Less Severe MGD	More Severe MGD	All	Less Severe MGD	More Severe MGD
N	115	59	56	120	55	65
<b>Age (years)</b>						
Mean (sd)	57.2 (13.9)	57.1 (13.2)	56.2 (14.6)	54.7 (14.7)	54.1 (14.8)	55.3 (14.4)
<b>Gender</b>						
Female	85/115 (74%)	43/59 (73%)	43/56 (77%)	83/120 (69%)	40/55 (73%)	43/65 (66%)
Male	29/115 (25%)	16/59 (27%)	12/56 (23%)	37/120 (31%)	15/55 (27%)	22/65 (34%)
<b>Ethnicity</b>						
Non-Hispanic or Latino	93/115 (81%)	49/59 (83%)	45/56 (80%)	101/120 (84.2%)	48/55 (87%)	54/65 (83%)
Hispanic or Latino	21/115 (18%)	10/59 (17%)	11/56 (20%)	19/120 (15.8%)	7/55 (13%)	11/65 (17%)

## DED Symptom Improvements

Raw results data of groups and subgroups on the total scores of each questionnaire are presented in [Table 2](#).

### OSDI

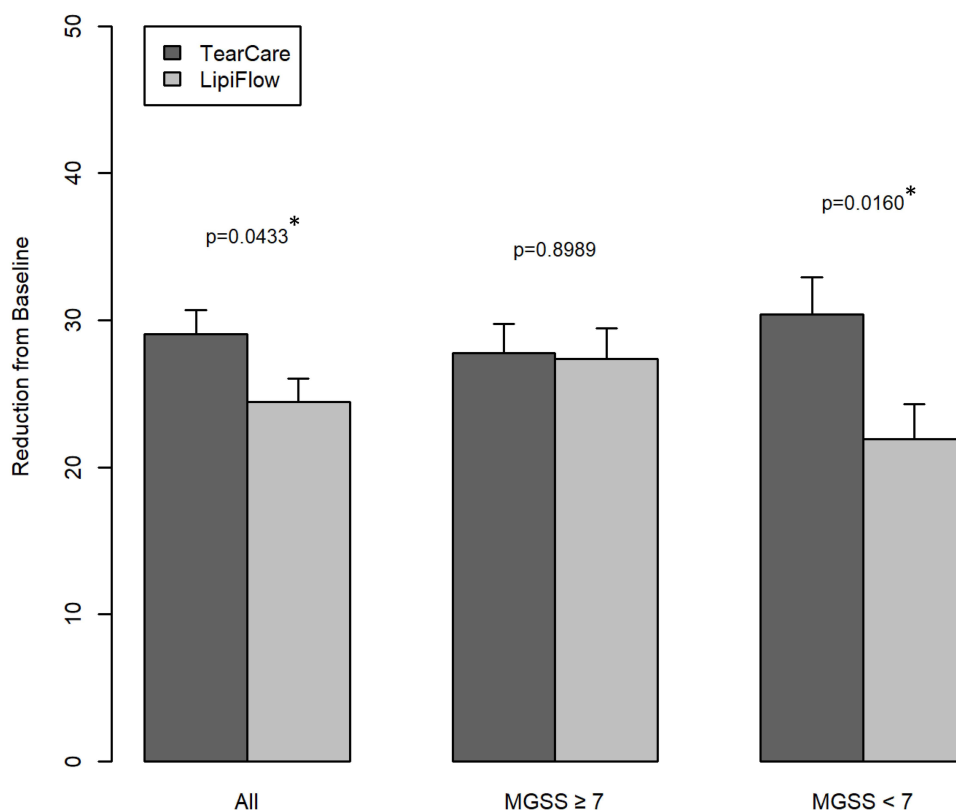
In all randomized subjects, both TearCare and LipiFlow procedures demonstrated statistically significant improvements compared to baseline in MGD-related symptoms of DED as measured by OSDI 1-month post-procedure ( $p < 0.0001$ ). The reduction from baseline OSDI score as expressed by least-squared (LS) mean and standard errors (SE) was  $29.1 \pm 1.62$  for subjects treated with TearCare (95% CI = [25.9, 32.2]) and  $24.4 \pm 1.59$  for subjects treated with LipiFlow (95% CI = [21.3, 27.6]). The reduction from baseline total OSDI score achieved with TearCare was significantly greater than the reduction achieved with LipiFlow (LS mean difference =  $4.6 \pm 2.27$ , 95% CI = [0.1, 9.1],  $p_{\text{ANCOVA}} = 0.0433$ ) ([Figure 1](#)). Analysis on each OSDI subsection revealed similar significant results favoring TearCare treatment in improving OSDI Section A (ocular symptoms). TearCare reduced OSDI Section A score by  $5.1 \pm 0.31$  (95% CI = [4.5, 5.7]), and LipiFlow reduced OSDI Section score by  $4.1 \pm 0.31$  (95% CI = [3.4, 4.7]). The treatment difference between the TearCare group and LipiFlow group was  $1.0 \pm 0.44$  (95% CI = [0.2, 1.9],  $p_{\text{ANCOVA}} = 0.0201$ ) ([Figure 2A](#)).

**Table 2** Differences in the Improvement in Symptoms at 1 Month from Baseline in TearCare and LipiFlow Groups and Less Severe and More Severe Disease Subgroups

Groups	TearCare			LipiFlow		
	All	Less Severe MGD MGSS $\geq 7$	More Severe MGD MGSS $< 7$	All	Less Severe MGD MGSS $\geq 7$	More Severe MGD MGSS $< 7$
<b>N</b>	115	59	56	120	55	65
<b>OSDI score Mean (sd)</b>						
Baseline	51.7 (14.79)	49.9 (14.69)	53.6 (14.78)	51.7 (15.27)	50.9 (15.65)	52.4 (15.03)
1 month	22.6 (17.21)	22.5 (14.74)	22.7 (19.62)	27.1 (18.97)	23.4 (17.45)	30.4 (19.74)
Mean improvement from baseline	-29.1 (20.60)	-27.3 (18.20)	-31.0 (22.88)	-24.4 (18.48)	-27.9 (18.08)	-21.4 (18.44)
Difference in improvement (TC-LF)	<b>4.7 (2.39)</b> <b><math>p = 0.05</math></b>	0.6 (3.43) $p = 0.6$	<b>9.6 (3.81)</b> <b><math>p = 0.01</math></b>			
<b>SANDE score Mean (sd)</b>						
Baseline	70.6 (16.78)	67.5 (20.38)	70.6 (16.78)	77.2 (15.82)	73.6 (15.59)	77.2 (15.82)
1 month	29.4 (26.58)	34.0 (28.19)	24.7 (24.12)	34.0 (28.06)	31.8 (27.36)	35.9 (28.72)
Mean improvement from baseline	-41.2 (28.43)	-33.2 (28.92)	-46.4 (26.50)	-43.2 (27.64)	-42.2 (26.19)	-41.1 (29.03)
Difference in improvement (TC-LF)	-1.9 (3.70) $p = 0.6$	8.9 (5.23) $p = 0.07$	<b>5.4 (5.14)</b> <b><math>p = 0.01</math></b>			
<b>ED score Mean (sd)</b>						
Baseline	69.9 (20.15)	68.2 (21.52)	71.7 (18.62)	71.9 (18.48)	70.7 (18.69)	72.9 (18.39)
1 month	31.5 (28.32)	35.2 (29.83)	27.6 (26.33)	35.0 (27.82)	33.0 (27.76)	36.7 (27.99)
Mean improvement from baseline	-38.4 (31.53)	-32.8 (32.32)	-44.3 (29.84)	-36.9 (27.87)	-38.2 (28.38)	-35.9 (27.60)
Difference in improvement (TC-LF)	1.5 (3.92) $p = 0.5$	-5.4 (5.76) $p = 0.3$	8.5 (5.29) $p = 0.08$			

**Notes:** Significant values are in bold.

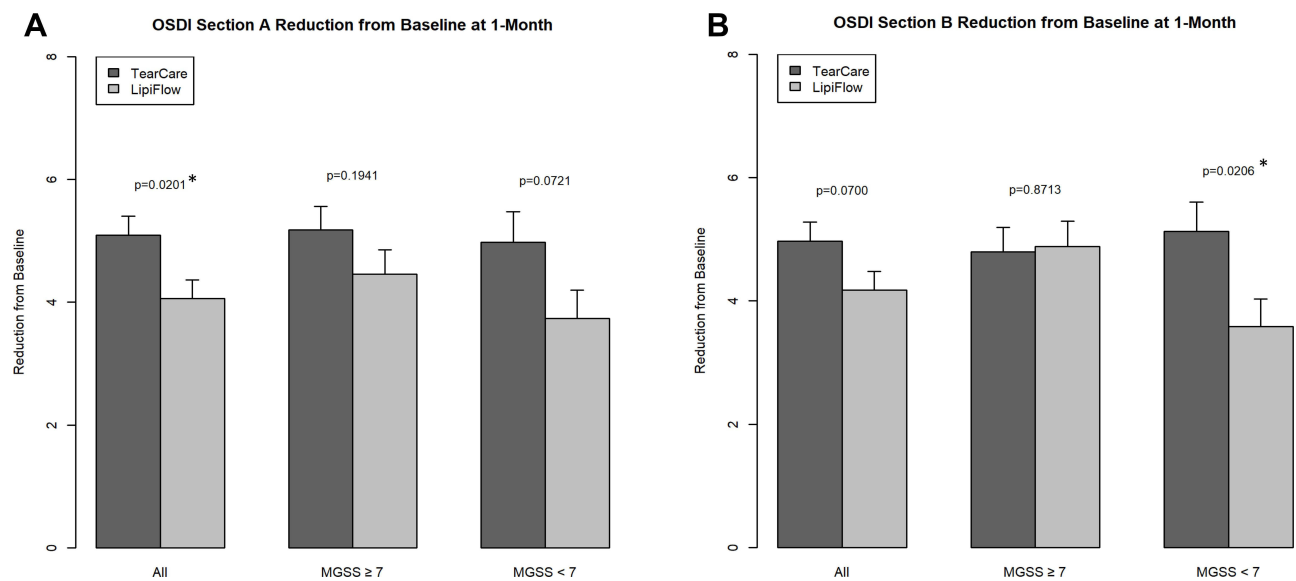
## OSDI Reduction from Baseline at 1-Month



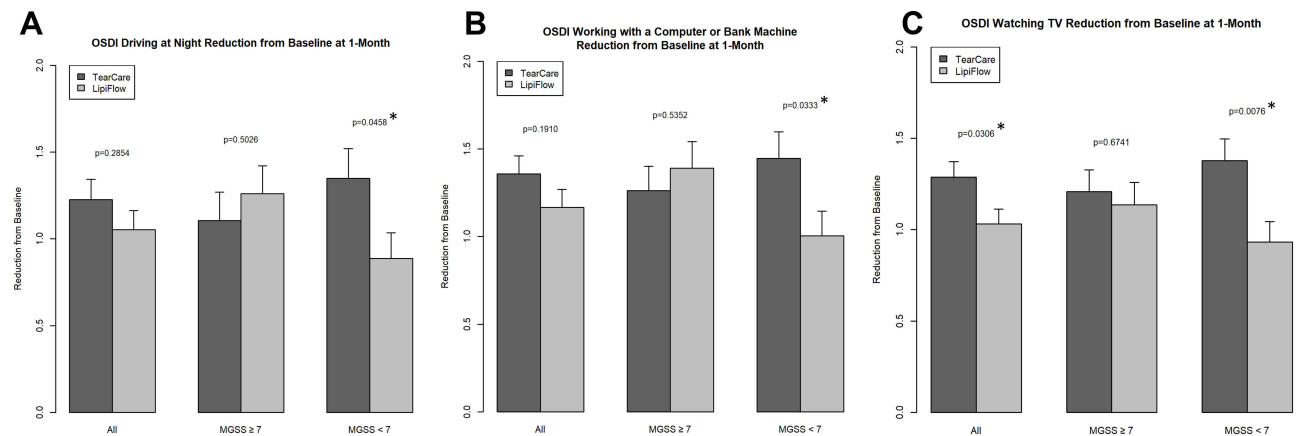
**Figure 1** TearCare demonstrated significant Ocular Surface Disease Index (OSDI) score reduction compared to LipiFlow in all subjects and in subgroup with Meibomian Gland Secretion Score (MGSS) <7. Bar graphs represent the mean reduction from baseline in OSDI score. Error bars represent the standard errors. The reduction from baseline total OSDI score achieved with TearCare was significantly greater than the reduction achieved with LipiFlow (LS mean difference =  $4.6 \pm 2.27$ , 95% CI = [0.1, 9.1],  $p_{\text{ANCOVA}} = 0.0433$ ). In subgroup with MGSS <7, the LS mean difference was  $8.5 \pm 3.47$ , 95% CI = (1.5, 15.4),  $p_{\text{ANCOVA}} = 0.0160$ . \*Indicates statistically significant  $p$  values.

In the subgroup analysis, TearCare demonstrated greater treatment effect in total OSDI score at 1 month with statistical significance in subjects experiencing more severe meibum and meibomian gland dysfunction at baseline (MGSS <7) in comparison to LipiFlow ( $p_{\text{ANCOVA}} = 0.0160$ ) (Figure 1). At 1-month follow-up visit, the reduction from baseline in total OSDI score was  $30.4 \pm 2.53$  (95% CI = [25.4, 35.4]) for subjects treated with TearCare and  $21.9 \pm 2.37$  (95% CI = [17.2, 26.6]) for subjects treated with LipiFlow. For the same subgroup, TearCare also performed significantly better than LipiFlow in improving OSDI Section B score that assessed visual functions specifically (LS mean difference =  $1.5 \pm 0.65$ ,  $p_{\text{ANCOVA}} = 0.0206$ ). The reduction from baseline in OSDI Section B score was  $5.1 \pm 0.48$  (95% CI = [4.2, 6.1]) for the TearCare group and  $3.6 \pm 0.45$  (95% CI = [2.7, 4.5]) for the LipiFlow group (Figure 2B). Specifically, in comparison to LipiFlow, TearCare provided better improvements in the following functions: driving at night (LS mean difference =  $0.5 \pm 0.23$ , 95% CI = [0.0, 0.9],  $p_{\text{ANCOVA}} = 0.0458$ ), working with a computer or bank machine (LS mean difference =  $0.4 \pm 0.21$ , 95% CI = [0.0, 0.8],  $p_{\text{ANCOVA}} = 0.0333$ ), and watching TV (LS mean difference =  $0.4 \pm 0.16$ , 95% CI = [0.1, 0.8],  $p_{\text{ANCOVA}} = 0.0076$ ) (Figure 3).

In the subjects with less severe MGSS  $\geq 7$ , TearCare and LipiFlow were equivalent in significantly improving total OSDI score and each OSDI subsection's score from baseline ( $p < 0.0001$ ).



**Figure 2** TearCare demonstrated significant Ocular Surface Disease Index (OSDI) Section A reduction in all subjects and OSDI Section B in subgroup with Meibomian Gland Secretion Score (MGSS) <7 compared to LipiFlow. Bar graphs represent the mean reduction from baseline in OSDI score. Error bars represent the standard errors. **(A)** The reduction from baseline total OSDI score achieved with TearCare was significantly greater than the reduction achieved with LipiFlow (LS mean difference =  $1.0 \pm 0.44$  (95% CI = [0.2, 1.9],  $p_{\text{ANCOVA}} = 0.0201$ ). **(B)** In subgroup with MGSS <7, the LS mean difference was  $1.5 \pm 0.65$ , 95% CI = (0.2, 2.8),  $p_{\text{ANCOVA}} = 0.0206$ . \*Indicates statistically significant  $p$  values.



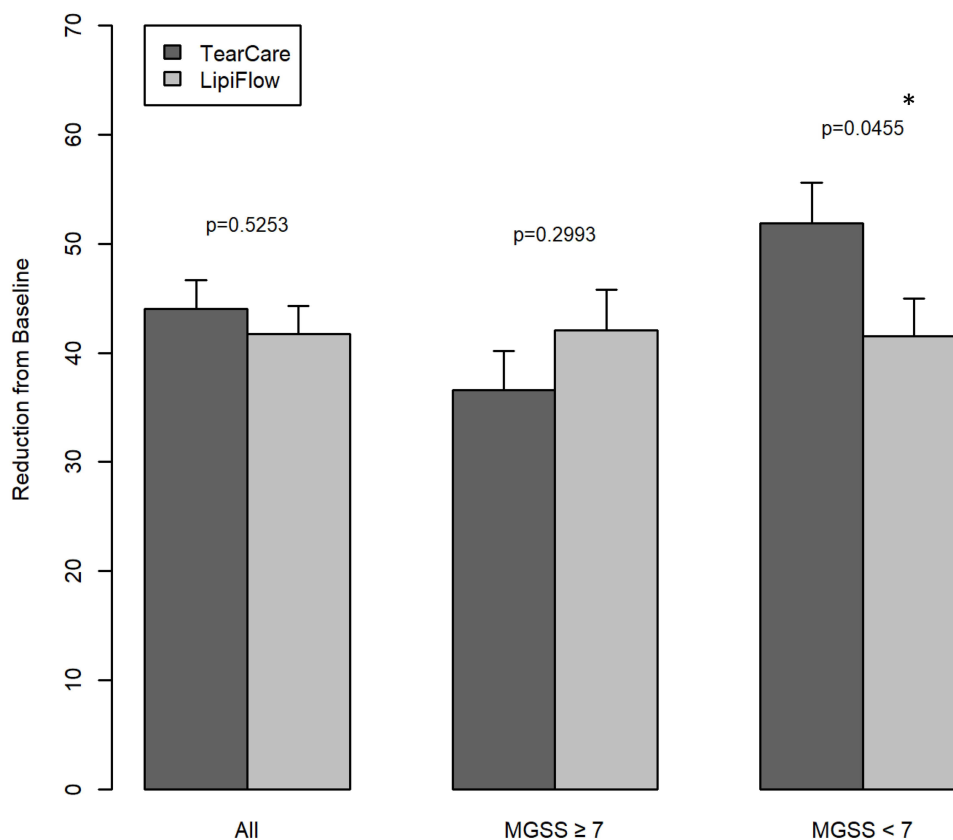
**Figure 3** TearCare provided better improvements in the following functions: driving at night, working with a computer or bank machine, and watching TV in subgroup with more severe disease. Bar graphs represent the mean reduction from baseline in OSDI score. Error bars represent the standard errors. **(A)** For driving at night, the LS mean difference was  $0.5 \pm 0.23$ , 95% CI = (0.0, 0.9],  $p_{\text{ANCOVA}} = 0.0458$ . **(B)** For working with a computer or bank machine, the LS mean difference was  $0.4 \pm 0.21$ , 95% CI = (0.0, 0.8),  $p_{\text{ANCOVA}} = 0.0333$ . **(C)** For watching TV, the LS mean difference was  $0.4 \pm 0.16$ , 95% CI = (0.1, 0.8),  $p_{\text{ANCOVA}} = 0.0076$ . \*Indicates statistically significant  $p$  values.

## SANDE

In all randomized subjects, TearCare and LipiFlow were equivalent in improving the total SANDE score as well as separate SANDE score for severity and frequency from baseline ( $p < 0.0001$ ). Similar results were obtained for the subgroup of subjects with less severe disease (MGSS  $\geq 7$ ).

Analysis in subgroup of subjects with more severe disease (MGSS <7) showed notable results. These subjects achieved higher numerical reduction of  $48.4 \pm 3.55$  (95% CI = [41.4, 55.4]) in total SANDE score with TearCare than with LipiFlow ( $39.3 \pm 3.31$  and 95% CI = [32.8, 45.9]) although the difference was not statistically significant ( $p_{\text{ANCOVA}} = 0.0673$ ). However, significantly better improvement was observed with TearCare in comparison to LipiFlow in this subgroup when SANDE frequency score was evaluated separately. The mean reduction from baseline in SANDE

### SANDE Frequency Reduction from Baseline at 1-Month



**Figure 4** TearCare decreased dry eye frequency assessed by Symptom Assessment Questionnaire in Dry Eye (SANDE) in the subgroup with more severe disease. Bar graphs represent the mean reduction from baseline in SANDE frequency score. Error bars represent the standard errors. The mean reduction from baseline in SANDE frequency score was  $51.9 \pm 3.70$  (95% CI = [44.5, 59.2]) for the TearCare group and  $41.5 \pm 3.45$  (95% CI = [34.7, 48.3]) for the LipiFlow group with LS mean difference =  $10.4 \pm 5.13$  and  $p_{\text{ANCOVA}} = 0.0455$ . \*Indicates statistically significant  $p$  values.

frequency score was  $51.9 \pm 3.70$  (95% CI = [44.5, 59.2]) for the TearCare group and  $41.5 \pm 3.45$  (95% CI = [34.7, 48.3]) for the LipiFlow group with LS mean difference =  $10.4 \pm 5.13$  and  $p_{\text{ANCOVA}} = 0.0455$  (Figure 4). In terms of SANDE severity score, although statistically significant difference was not established between the two treatment groups ( $p_{\text{ANCOVA}} = 0.1028$ ), these subjects trended toward better improvement using TearCare treatment with numerical mean reduction of  $44.6 \pm 3.60$  (95% CI = [37.5, 51.8]) compared to  $36.5 \pm 3.36$  (95% CI = [29.8, 43.2]) with LipiFlow treatment.

### Eye Dryness Score

Significant improvements from baseline in ED scores ( $p < 0.0001$ ) were demonstrated for all randomized subjects, subgroup with less severe disease (MGSS  $\geq 7$ ), and subgroup with more severe disease (MGSS  $< 7$ ). TearCare and LipiFlow showed no statistically significant difference between two groups. In the subgroup with more severe disease (MGSS  $< 7$ ), although the difference between two treatment groups was not significant, the treatment effect seemed to trend in favor of TearCare with LS mean difference of  $8.9 \pm 4.87$  (95% CI = [0.8, 18.5]) and  $p$ -value of 0.0713.

### Discussion

The results presented in this report showed that a single treatment of LipiFlow and TearCare can significantly improve DED symptoms in adult patients with MGD with added benefits from TearCare in certain populations. Subjects treated with TearCare achieved similar reduction compared to the active-control, LipiFlow, in total OSDI score, total SANDE

score, and ED score for all randomized subjects. Post-hoc subgroup analysis in the less severe group and more severe group based on median MGSS provided further understanding of the treatment effect favoring TearCare for DED symptom improvement. Subjects with more severe meibomian gland dysfunction achieved greater significant improvements in total OSDI, OSDI subsection focusing on quality of vision, and SANDE frequency score with TearCare in comparison to LipiFlow. Results of other assessments including OSDI subsections on ocular symptoms and environmental triggers, total SANDE score, SANDE severity score, and ED score also trended toward more reduction with TearCare although statistical significance was not attained. These results suggested that TearCare not only is beneficial for all patients regardless of MGD severity but also can offer additional meaningful DED symptom relief to the subjects with more severe blockages in the meibomian gland. For subjects with less severe blockage in the meibomian gland, both LipiFlow and TearCare presented as effective treatments since the two devices significantly reduced the total OSDI score, OSDI subsection scores, total SANDE score, and SANDE score for severity and frequency from baseline.

Maintaining a healthy lipid layer plays a critical role in preventing evaporative DED.<sup>17,18</sup> The TearCare system delivers precise heat to the tarsal plates of upper and lower eyelids and meibomian glands with the SmartHub controller, and facilitates the manual expression of subjects' meibomian glands with its Clearance Assistant units to enhance the natural flow of lipids. LipiFlow system uses a Console and a single-use sterile device called Activator to apply heat to the palpebral surfaces of the upper and lower eyelids directly over the meibomian glands after a local anesthetic drop is instilled. Simultaneously, graded pulsatile pressure is applied to the outer eyelid surfaces, thereby expressing the meibomian glands in closed eyes during heating. The TearCare system delivers to the outer eyelid surfaces and thus allows normal blinking with its SmartLid units and does not use an initial anesthetic drop. Both systems utilize heat and pressure applications as the mechanism of action; however, all applications are embedded in one system with LipiFlow while with TearCare, there is an additional unit used to further express the meibomian gland manually by clinicians. The mechanisms described in both devices helps tear film to recover as the gland blockage is cleared. Consequently, DED improves as demonstrated by positive outcomes in DED symptom assessments presented here and also in DED sign assessments such as TFBUT, fluorescein staining, etc. in earlier studies.<sup>11,12</sup>

This study provided reliable data in terms of symptom evaluations with different assessment tools. Previous efficacy data on symptom improvements were limited as the majority of currently available DED treatments such as Restasis<sup>®</sup>, Xiidra<sup>®</sup>, and CEQUA<sup>™</sup> were mostly approved based on sign efficacy endpoints.<sup>7-9</sup> Here, symptom improvements are highlighted across multiple reliable assessment measurements. Consistent results supporting TearCare efficacy were observed in not only ED score, overall SANDE score, and OSDI but also in each subsection of the SANDE questionnaire (frequency and severity) and OSDI questionnaire (ocular symptoms, vision-related functions, environmental triggers) for both the analysis in all randomized subjects and in subgroups. Utilizing multiple questionnaires offers additional benefits because besides symptom assessment, and some questionnaires such as OSDI also incorporate quality of life measures that can capture patient perspectives on treatment effectiveness more comprehensively. Such questionnaires are highly encouraged as the US Federal Food and Drug Administration promoted the use of patient-reported outcomes to support clinical trials and product submissions. Based on this report, TearCare successfully provided clinically meaningful improvements in both dry eye symptoms and vision-related functions to have positive impact on patients' lives.

In addition, delayed onset of action of several months associated with currently available anti-inflammatory treatments is the most prevalent factor leading to low treatment satisfaction in both physicians and patients.<sup>19,20</sup> A study in 2020 reported that only 10% and 48% of physicians were satisfied with the onset of action for cyclosporine ophthalmic emulsion 0.05% and lifitegrast 5% ophthalmic solution, respectively.<sup>18</sup> Similarly, patients also perceived low satisfaction with onset of action for current treatments: only 51% of patients on cyclosporine ophthalmic emulsion and 63% of patients on lifitegrast ophthalmic solution reported being satisfied.<sup>19</sup> Low level of satisfaction can negatively affect overall treatment compliance and effectiveness. Therefore, DED treatment options with faster onset are needed. In this study, TearCare demonstrated remarkable onset of action for symptom relief at 1-month follow-up. This result aligns well with previously reported efficacy studies in TearCare. Prior studies proved TearCare to be more effective than warm compress in improving both DED signs and symptoms at 1-month timepoint and maintaining such effects for up to 6 and 12 months.<sup>11,12</sup> An exploratory study in 2020 described significant improvements in OSDI achieved with TearCare as

early as at 1-week follow-up visit and continued to improve further at 1-month visit.<sup>13</sup> Early onset of action is a notable advantage that sets TearCare apart as an effective treatment option for DED. One limitation of this current study is the short follow-up duration of 1 month.

In summary, both LipiFlow and the TearCare system consistently improved DED symptoms assessed by total OSDI, SANDE, and Eye Dryness score from baseline. Furthermore, the subject population with severe gland obstructions and in need for a better gland clearance, achieved greater meaningful symptom relief with TearCare in comparison to LipiFlow. In subjects with more severe meibomian gland dysfunction, TearCare provided better improvements in overall symptom relief, vision-related functions, and DED symptom frequency expressed by total OSDI score, OSDI Section B score, and SANDE frequency score. With the benefits of fast action onset and excellent efficacy in symptomatic relief, the TearCare system presents as a compelling option for DED treatment among currently available treatments.

## Abbreviations

OSDI, Ocular Surface Disease Index; TBUT, Tear-film Break-Up Time; MGSS, Meibomian Gland Secretion Score; MGD, Meibomian Gland Dysfunction; CI, Confidence Intervals; DED, Dry Eye Disease; SANDE, Symptom Assessment In Dry Eye.

## Data Sharing Statement

The authors do not intend to share participant-level data.

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## Disclosure

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