



# The Efficacy and Safety of New-Generation Intense Pulsed Light in the Treatment of Meibomian Gland Dysfunction-Related Dry Eye: A Multicenter, Randomized, Patients-Blind, Parallel-Control, Non-Inferiority Clinical Trial

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## ABSTRACT

**Introduction:** This study aimed to evaluate the efficacy and safety of a new-generation intense pulsed light (IPL) device in improving the symptoms and signs of meibomian gland dysfunction (MGD)-related dry eye, and compare it with a traditional IPL device.

**Methods:** This multicenter randomized controlled trial enrolled 132 patients with MGD-related dry eye from two centers. Patients were randomly assigned into the new-generation IPL (Eyesis) group or traditional IPL (E-Eye) group, and then blinded to receive treatment on days 0 and 7. Ocular Surface Disease Index (OSDI), tear

meniscus height (TMH), tear breakup time (TBUT), corneal fluorescein staining (CFS), Schirmer test, and meibomian gland signs were evaluated on days 0, 7, and 14. The primary outcome was defined as the effective rate of treating MGD at day 14. Any adverse events were recorded for safety assessment. Intergroup comparisons and non-inferiority analysis were performed.  $p$  values less than 0.05 were considered statistically significant.

**Results:** Basic information showed no significant difference between treatment groups. The intergroup difference of the effective rate was  $-1.7\%$  in the left eye and  $1.6\%$  in right eye, verifying the non-inferiority of the Eyesis device ( $p = 0.927$ ). Significant improvements in OSDI, TBUT, Schirmer test, TMH, CFS, and meibomian gland signs were observed in Eyesis group on days 7 and 14 (all  $p < 0.05$ ). Compared to the E-Eye group, the Eyesis group achieved more significant improvements in OSDI, TBUT, Schirmer test, TMH, and meibum quality (all  $p < 0.05$ ). There was no significant difference in the incidences of adverse events between groups ( $p = 1.000$ ).

**Conclusions:** The new-generation IPL was effective and safe in relieving the symptoms and signs of MGD-related dry eye, exhibiting a non-inferior effective rate compared to the traditional IPL. Additionally, Eyesis showed more clinical benefits over E-Eye in alleviating symptoms, increasing tear film stability and improving meibomian gland function.

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**Keywords:** Dry eye; Intense pulsed light; Meibomian gland dysfunction; Tear film

### Key Summary Points

#### *Why carry out this study?*

The efficacy and safety of the Eysis intense pulsed light (IPL) device, a new-generation IPL device with a wider energetic intensity range, in the treatment of meibomian gland dysfunction (MGD) have not been determined.

The impact of wavelength, energy intensity, and pulse width on the efficacy of IPL treatment has not been explored.

This study aimed to determine what the efficacy and safety of the new-generation IPL device is in improving the symptoms and signs of MGD, and how it compares to a traditional IPL device.

#### *What was learned from the study?*

The intergroup difference of the effective rate in MGD treatment was – 1.7% (95% CI – 5.07% to 1.63%) in left eyes and 1.6% (95% CI – 1.64% to 4.82%) in right eyes, verifying the non-inferiority of the Eysis device.

Eysis was effective and safe in relieving MGD, exhibiting a non-inferior effective rate compared to the traditional device, and different machine parameters might decide the treatment effect.

Eysis showed more clinical benefits in alleviating symptoms, increasing tear film stability, stimulating tear secretion, and improving meibomian gland function.

## INTRODUCTION

Meibomian gland dysfunction (MGD) is a chronic disease of meibomian glands characterized by the obstruction of terminal ducts and

the qualitative or quantitative abnormality of meibum secretion [1]. As one of the most common disorders encountered in ophthalmic clinics, the prevalence of MGD ranges from 3.5% to 70% worldwide [2]. The hyperkeratosis of ductal epithelium, increased viscosity of meibum, and rising melting points of gland secretions can predispose towards obstruction and inflammation of the ductal system, thereby resulting in intraglandular cystic dilation, gland dropout, and low secretion [3, 4]. The consequent reduction of meibum compromises the integrity of the surface lipid layer and boosts the proliferation of commensal bacteria, eventually causing a vicious circle of tear film hyperevaporation, instability, hyperosmolarity, and inflammation [5, 6]. MGD may occur as an isolated disorder, but it is often accompanied by dry eye disease (DED) which is classified as “MGD-related DED” by the International Workshop on MGD [7]. DED is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film [8]. Tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles in DED [6]. On the basis of the pathogeny, DED could be divided into evaporative and aqueous-deficiency subtypes [8], and MGD is one of the most common causes of evaporative DED [7]. It is reported that 32.9% of patients with dry eye is related to MGD by the Dry Eye Workshop II (DEWS II) [9].

Currently, an increasing number of treatments have been available for MGD-related dry eye, mainly including artificial tear supplements, warm compress, meibomian gland expression (MGX), antibiotics, anti-inflammatory and immunomodulatory agents [10, 11]. Despite the variety of therapeutic methods, however, many patients with MGD are refractory to treatment and it is frequently difficult to achieve or sustain complete or long-term relief of their symptoms. Therefore, more optional and effective treatments are gradually coming into view, one of which is intense pulsed light therapy [12].

Intense pulsed light (IPL) therapy was initially applied in the cosmetic industry and dermatological diseases, including hypertrichosis,

benign cavernous hemangiomas, venous malformations, telangiectasia, and other pigmented lesions [13–16]. IPL devices adopt xenon flash lamp to emit high-intensity polychromatic light, ranging from the visible to infrared spectrum, to target various chromophores such as hemoglobin, melanin, and water [17]. The wavelength, penetration depth, and targeted areas can be tailored for selective thermal delivery to specific structures [18]. In 2002, a serendipitous report that a patient with facial rosacea presented improvements of dry eye symptoms after receiving IPL treatment indicated that IPL treatment might be a potential treatment for MGD [19]. Since then, several clinical trials have preliminarily demonstrated that IPL is an effective treatment for improving subjective symptoms and objective signs in patients with MGD-related DED [20–26]. However, the ranges and grading levels of the pulse intensity in traditional IPL devices were limited and mainly determined by the individual skin color that was uncorrelated with the severity of MGD. Therefore, traditional IPL treatment might be imprecise and poorly targeted, and its efficacy for critical and refractory MGD was uncertain. For the optimization, as shown in Table 1, Eysis IPL device (MDC, Beijing, China), a new-generation IPL device with calibrated intense regulated pulsed light (IRPL) delivered under the “smile” shape (illustrated in the Supplementary Material), is designed with a wider energetic intensity range and could

deliver more precise pulse intensity based on both skin phenotype and MGD severity. Nevertheless, the efficacy and safety of Eysis in the treatment of MGD-related dry eye have not been determined yet. On the other hand, according to previous reports, three different traditional devices have been clinically applied for IPL treatment, namely E-Eye (E-Swin, Paris, France) [20, 27, 28], M22 (Lumenis, Yokneam, Israel) [25, 26, 29, 30], and Q4 (DermaMed Solutions, LLC, Lenni, USA) [31]. The variety of wavelength, energy intensity, and pulse width among these devices resulted in different efficacy and safety during IPL treatment, which have not been explored and compared until now.

This multicenter, randomized, patient-blinded, controlled trial aimed to evaluate the efficacy and safety of the Eysis IPL device in improving the symptoms and signs of MGD-related dry eye, and compare its effective rate with the traditional E-Eye IPL device as an active control to verify the non-inferiority.

## METHODS

### Subject Recruitment and Ethics Compliance

This multicenter, randomized, patient-blinded trial adhered to the tenets of the Declaration of Helsinki and was approved by the Human

**Table 1** Comparison of instrument parameters between the new-generation IPL device (Eysis device) and the traditional IPL device (E-Eye device)

	Eysis device	E-Eye device
Range of energy intensity	5–15 J/cm <sup>2</sup>	9–13 J/cm <sup>2</sup>
Grading strategy of energy intensity	21 grading levels based on MGD severity and skin color	6 grading levels based on skin color
Range of wavelength	580–1200 nm	580–1200 nm
Number of pulses per cluster	10 pulses per cluster	Two-time 3.5 pulses per cluster
Shape of IRPL	Regulated “smile” pulses	Regulated “train” pulses
Refrigeration of operation head	Active refrigeration	No

IRPL intense regulated pulsed light, MGD meibomian gland dysfunction

Research and Ethics Committee of Peking University Third Hospital and Wangjing Hospital of Chinese Academy of Traditional Chinese Medicine. Written informed consents were obtained from all patients before enrollment. Patients with diagnosed MGD were consecutively recruited from the Department of Ophthalmology in Peking University Third Hospital (center A) and Wangjing Hospital of Chinese Academy of Traditional Chinese Medicine (center B) between January 2020 and June 2020.

The sample size was determined by NCSS PASS 2002 software (Utah, USA), with 80% power ( $\beta = 0.2$ ) and a two-side statistical significance level of 5% ( $\alpha = 0.05$ ). The effective rate of treatment in MGD-related dry eye on day 14 was regarded as the primary outcome. According to our previous study and clinical experience [20, 23–27], the effective rates of the Eysis device and E-Eye device were preliminarily estimated as 85% and 75%, respectively, and the non-inferiority margin of the effective rate was defined as 10%. Based on an assumed dropout rate of 5%, calculations showed that a sample size of 132 patients was needed in our trial (66 patients in the Eysis group and 66 patients in the E-Eye group).

The inclusion criteria for the study were (1) adults aged between 18 and 80 years; (2) chief complaint of one of the following symptoms: dryness, foreign body sensation, burning, and tearing for more than 3 months; (3) diagnosis of MGD in both eyes based on the criterion proposed by the Tear Film and Ocular Surface Society (TFOS) [7, 32]: abnormal morphologic lid features (i.e., redness or thickening of the lid margin, telangiectasia, glandular orifice obstruction) and/or alterations of meibomian gland secretion (i.e., reduced or no secretions, poor quality secretions); (4) willingness to cooperate in the follow-up visits.

The exclusion criteria included patients with (1) contact lens use within the past 1 month; (2) use of any eye drops other than artificial tears within the past 3 months; (3) history of ocular trauma or surgery; (4) IPL treatment or any equivalent treatments within the past 12 months; (5) current use of treatments for MGD; (6) uncontrolled allergy, infection, or

inflammatory disease on the ocular surface unrelated to dry eye or MGD; (7) current use of punctual plugs or alterations of the lacrimal drainage system; (8) uncontrolled systemic disease or systemic diseases affecting the ocular surface; (9) systemic medications altering the tear film; (10) precancerous lesions, skin cancer, or pigmented lesions in the planned treatment area; (11) no contraindications to IPL therapy, including the use of photosensitive medications; (12) pregnancy and lactation. After screening, all eligible patients were voluntarily included in the study.

### Treatments Procedure

According to the random numbers generated by the PROC PLAN randomization procedure in SAS 9.2 (Cary, NC, USA), all patients who met the inclusion and exclusion criteria were randomly assigned into Eysis IPL treatment group (group A) or E-Eye IPL treatment group (group B). The intergroup allocation ratio was 1:1 and patients were blinded to the assignment. The randomization sequence was put in an opaque sealed envelope. The allocation assignment was uncovered during the process of IPL treatment, clinical evaluation and data collection, and was eventually revealed in the statistical analysis.

IPL treatment was delivered twice in all enrolled patients separately with an interval of 1 week on day 0 and day 7. In group A, IPL treatment was administered bilaterally by the new-generation IPL device Eysis (MDC, Beijing, China). The pulse intensity of Eysis ranged from 5 to 15 J/cm<sup>2</sup> and was determined by the combination of Fitzpatrick Skin Type Grading [27] and Meibum Quality Grading [7] (see Supplementary Material for details). In group B, patients underwent bilateral IPL treatment provided by the traditional IPL device E-Eye (E-Swin, Paris, France). The intensity of E-Eye ranged from 9.8 to 13 J/cm<sup>2</sup> according to the individual skin phenotype level determined by the Fitzpatrick Skin Type Grading [27] (see Supplementary Material for details). Before treatment, protective opaque goggles were placed on both eyes and clear conducting gel

was applied on the patient's periocular area to conduct the light and spread the energy evenly [31]. In each IPL treatment, five overlapping flashes were applied to the skin area below the lower eyelid for every eye with no pressure. The upper eyelid was not treated directly to avoid possible light damage to the intraocular structures. All the treatments were performed by a trained clinician (XDJ), who was not involved in data collection and statistics analysis. Mechanical meibomian gland expression was not allowed in the study period.

### Clinical Evaluation

Clinical evaluations were conducted immediately before the IPL treatment on day 0, 1 week after the first treatment course on day 7, and 2 weeks after the first treatment course on day 14. To assess the improvement of subjective symptoms, the Ocular Surface Disease Index (OSDI) questionnaire was administered to patients. To evaluate the change of ocular signs, clinical measurements were performed in ascending order of invasiveness: conjunctival examination, lower tear meniscus height (TMH), tear breakup time (TBUT), corneal fluorescein staining (CFS), Schirmer test, lid margin, and meibomian gland assessments [20, 24]. An interval of 5 min was required between different tests. All the measurement data were collected and recorded by two doctors (MZZ and HY) and the average was regarded as the final result.

#### *Conjunctival Examination and TMH*

Conjunctival hyperemia and conjunctivochalasis were evaluated under a slit-lamp microscope. The degree of conjunctival hyperemia was determined by Institute for Eye Research (IER) Grading Scales [33, 34], which assessed bulbar conjunctival redness with grade 0 meaning no redness and group 3 representing severe diffuse injection. The level of conjunctivochalasis was graded on the basis of lid-parallel conjunctival folds (LIPCOF) [35], with group 0 representing no persistent fold and group 3 indicating multiple folds and higher than the torn meniscus. The central lower TMH was observed and measured by a slit-lamp

microscope with a graticule in 0.1-mm units, scaring from 0 to 0.3 mm and grading from group 0 (0 mm) to group 3 (0.3 mm).

#### *TBUT, CFS, and Schirmer Test*

A total of 5  $\mu$ L of 2% sodium fluorescein was softly instilled onto the bulbar conjunctiva by a fluorescein sodium ophthalmic strip, without inducing reflex lacrimal secretion. The patient was asked to blink naturally for three to five times, and then stare straight ahead under the cobalt blue light without blinking, to count the time interval between the last complete blink and the appearance of the first disruption in the tear film [36]. TBUT was measured three times for each patient and the average value was taken as the final result. Corneal fluorescein staining was evaluated on the basis of the grading system proposed by Ogawa et al. [37], ranging from group 0 to group 3 (group 0, no staining; group 1, minimal staining; group 2, mild/moderate staining; group 3, severe staining). Schirmer test included placing the folded portion of a filter paper strip in the conjunctiva sac at the outer one third of the lower eyelid. The amount of wetted part in the strip was recorded in millimeters after 5 min [36].

#### *Lid Margin and Meibomian Gland Assessments*

Lid margin telangiectasia/vascularity and irregularity/notching of margin were evaluated in our study under a slit-lamp microscope. The results were recorded as "absent/normal" or "present/abnormal". Meibomian gland assessments were composed of meibomian gland expressibility (MGE), gland dropout, and meibum quality. MGE was determined by the expressibility test, in which the central five glands of the lower eyelid were pressed to observe the secretion of meibum (group 0, 5 glands expressing; group 1, 3–4 glands expressing; group 2, 1–2 glands expressing; group 3, 0 glands expressing) [7, 38]. The morphology of meibomian glands was observed by the OCU-LUS Keratograph 5M, and the severity of gland dropout was recorded using the 4-point grading scale as described by Arita et al. (group 0, no dropout; group 1, < 1/3 total area dropout;



group 2, 1/3–2/3 total area dropout; group 3, > 2/3 total area dropout) [38]. Meibum quality from the lower eyelid was divided into four degrees: 0, clear and fluid; 1, cloudy and fluid; 2, cloudy and granular; 3, whitish and toothpaste-like [7, 39].

### **MGD Staging**

To assess the severity of MGD-related dry eye, an experienced dry eye doctor (XML) provided an MGD staging evaluation for each patient after synthetically considering the severity of symptoms and clinical measurements (MGE, meibum quality, and CFS) as described by the International Workshop on MGD [3], grading from stage 0 to stage 4 (absent, mild, moderate, severe, and critical).

### **Safety Assessment**

The safety of treatment was evaluated by best corrected visual acuity (BCVA) and the incidence of adverse events. BCVA was recorded in the form of logMAR. Adverse events were evaluated by ophthalmological examination and periocular skin assessment. Ophthalmological examination was composed of examinations of the eyelid, eyelash, conjunctiva, cornea, lens, and fundus by a slit-lamp microscope. An evaluation of the periocular skin area was also carried out, including the assessment of depigmentation, blistering, swelling, redness, and hair loss at the brow and forehead.

### **Evaluation Criteria**

The primary outcome for efficacy was the effective rate in the treatment of MGD-related dry eye at the endpoint (day 14). The treatment outcome was classified as excellence, improvement, or failure depending on the improvements of objective symptoms, Schirmer test, TBUT, and the detailed classification criteria are shown in the Supplementary Material. The effective rate was calculated as the percentage of excellence cases combined with improvement cases. Given the non-inferiority margin was defined as 10%, the Eysis device would be considered non-inferior to the E-Eye device if

the lower 95% confidence interval limit of the intergroup difference of the effective rates (group A minus group B) was more than – 10%. The secondary outcomes for efficacy included OSDI, Schirmer test, TBUT, TMH, CFS, lid margin assessment, meibomian gland expressibility, gland dropout, meibum quality, and MGD staging. Safety was assessed according to BCVA and the incidences of adverse events.

### **Statistics Analysis**

SAS 9.3 (Cary, NC, USA) was applied to complete the data analysis. Continuous variables in our study were presented as mean  $\pm$  SD (standard deviation) and categorical variables were expressed as number and percentage. As the primary outcome, the effective rate at the endpoint was calculated with its 95% confidence interval (95% CI) and compared by Fisher's exact test between groups. Non-inferiority was assessed on the basis of the intergroup difference in the effective rates, with an inferiority margin of 10%. The non-inferiority would be confirmed if the lower limit of 95% CI was more than – 10%. The intergroup comparisons were performed by Mann–Whitney *U* test (for continuous variables and ranked categorical variables) and chi-square test (for disorder categorical variables). The intragroup comparisons between different points were conducted by Wilcoxon rank test (for continuous variables and ranked categorical variables) and McNemar test (for disorder categorical variables). To assess the safety, the incidences of adverse events at the endpoint were compared by Fisher's exact test between groups. Outcomes would be considered statistically significant if  $p < 0.05$ .

## **RESULTS**

### **Patient Information**

A total of 132 patients were enrolled in our study after recruiting and screening as shown in Fig. 1, including 66 patients from center A and 66 patients from center B. After exclusion of five patients because of the lack of treatment

records, 61 patients were analyzed in group A (29 female, 32 male), with a mean age of  $50.31 \pm 15.31$  years (range 24–80 years). After exclusion of one patient because of the lack of treatment records, 65 patients were analyzed in group B (39 female, 26 male), with a mean age of  $55.45 \pm 13.40$  years (range 23–79 years). The detailed demographic information is presented by treatment group in the Supplementary Material. Basic demographics did not differ between treatment groups (all  $p > 0.05$ ).

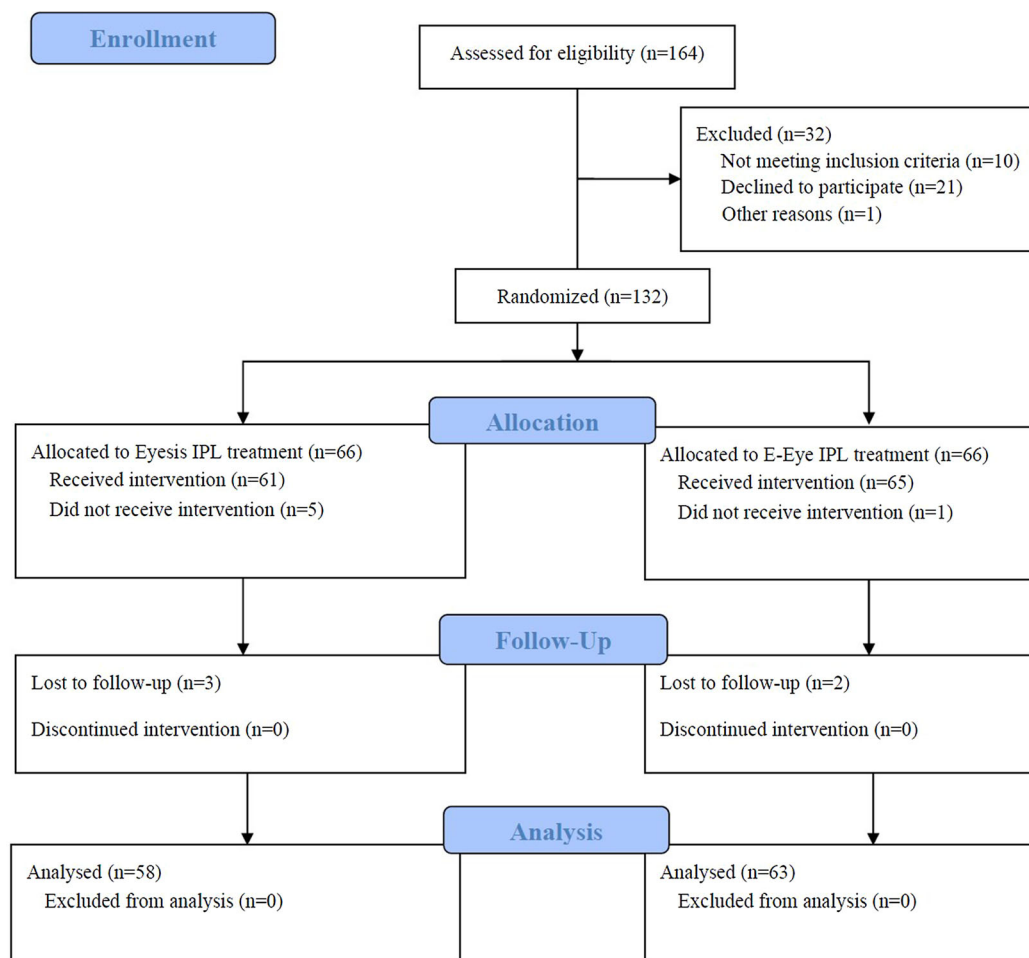
The results of clinical measurements at baseline are presented in the Supplementary Material. Comparing group B with group A, no significant difference was observed in BCVA, OSDI, TBUT, Schirmer test, TMH, conjunctival hyperemia, lid features, gland dropout, and

meibum quality between groups at baseline (all  $p > 0.05$ ). However, there was a significant difference in CFS ( $p = 0.033$ ) and MGD staging ( $p = 0.046$ ) of left eyes between the two groups at baseline.

**Efficacy Evaluation**

**Primary Outcome**

As illustrated in Fig. 1, three patients in group A and two patients in group B were lost to follow-up during the study period and excluded from the efficacy analysis. The results of treatment outcomes that combined objective symptoms, Schirmer test, and TBUT together at endpoint are shown in Table 2. Among 58 patients in group A, the effective rate of 14-day Eysis IPL



**Fig. 1** CONSORT flow diagram

**Table 2** Results of treatment outcomes and effective rates at endpoint in groups A and B

	<i>N</i>	Excellence ( <i>n</i> )	Improvement ( <i>n</i> )	Failure ( <i>n</i> )	Effective rate (%)	Difference of effective rate (%)	CL (%)	CU (%)	<i>p</i> value
L									
Group A	58	42	15	1	98.3	− 1.7	− 5.07 <sup>#</sup>	1.63	0.927
Group B	63	16	47	0	100.0				
R									
Group A	58	38	20	0	100.0	1.6	− 1.64 <sup>#</sup>	4.82	0.927
Group B	63	15	47	1	98.4				

L left eye, R right eye, CL lower limit of 95% confidence interval, CU upper limit of 95% confidence interval

<sup>#</sup>The lower limit of 95% confidence interval was more than − 10%, thereby verifying the non-inferiority of Eysis

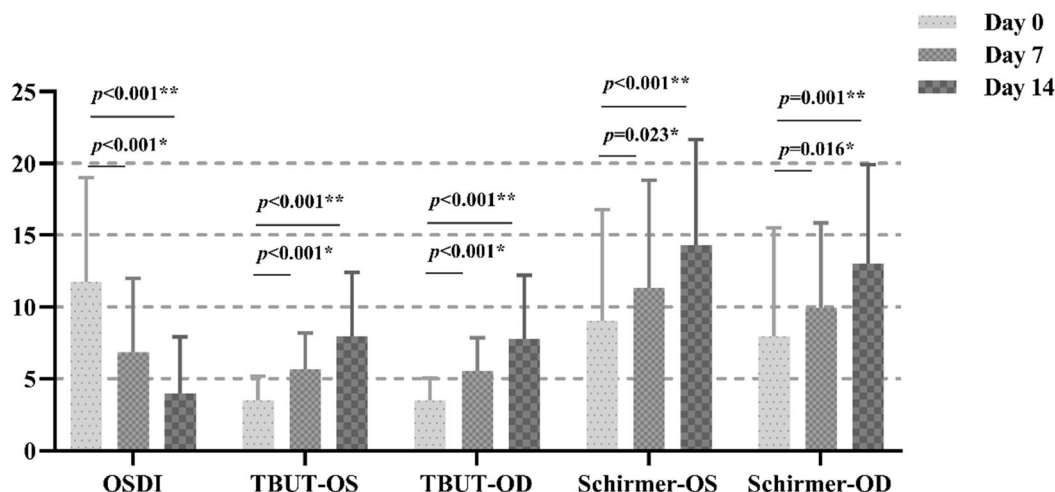
treatment in left eyes was 98.3% with 42 cases evaluated as excellence and 15 cases defined as improvement, and the effective rate in right eyes was 100.0% with 38 cases assessed as excellence and 20 cases regarded as improvement. Among 63 patients in group B, the effective rate of 14-day E-Eye IPL treatment in left eyes was 100.0% with 16 cases evaluated as excellence and 47 cases defined as improvement, and the effective rate in right eyes was 98.4% with 15 cases assessed as excellence and 47 cases regarded as improvement. Comparing the effective rates in the two groups (group A minus group B), the difference of left eyes was − 1.7% (95% CI − 5.07% to 1.63%) and the difference of right eyes was 1.6% (95% CI − 1.64% to 4.82%). No significant difference was observed in the effective rates of both eyes between groups (both  $p = 0.927$ ). The lower 95% CI limits of the effective rate difference between groups in both eyes did not exceed the predetermined non-inferiority limit of − 10%. Therefore, the non-inferiority of the Eysis device in the treatment of MGD-related dry eye was verified.

### Secondary Outcome

Figure 2 illustrates the intragroup comparisons of OSDI, TBUT, and Schirmer test between day 7, day 14, and baseline (day 0) in group A. OSDI after IPL treatment on day 7 ( $6.84 \pm 5.15$ ) and day 14 ( $3.98 \pm 3.95$ ) significantly decreased compared to that at baseline ( $11.78 \pm 7.24$ ) in group A (both  $p < 0.001$ ). Consistently, compared with the baseline (L,  $3.50 \pm 1.67$  s; R,  $3.46 \pm 1.58$  s), TBUT of both eyes in group A significantly lengthened after IPL treatment on day 7 (L,  $5.67 \pm 2.51$  s; R,  $5.53 \pm 2.34$  s; both  $p < 0.001$ ) and day 14 (L,  $7.97 \pm 4.43$  s; R,  $7.79 \pm 4.43$  s; both  $p < 0.001$ ). Compared with the baseline (L,  $9.04 \pm 7.72$  mm; R,  $7.94 \pm 7.55$  mm), the results of Schirmer test in both eyes were also remarkably improved on day 7 (L,  $11.33 \pm 7.49$  mm,  $p = 0.023$ ; R,  $9.93 \pm 5.92$  mm,  $p = 0.016$ ) and day 14 (L,  $14.28 \pm 7.39$  mm,  $p < 0.001$ ; R,  $13.04 \pm 6.86$  mm,  $p = 0.001$ ).

Figure 3 illustrates the intragroup comparisons of TMH, CFS, MGE, gland dropout, and meibum quality between day 7, day 14, and baseline (day 0) in group A. Compared to baseline, the lower TMH of both eyes got significantly higher at the visit of day 7 (both  $p < 0.001$ ) and day 14 (both  $p < 0.001$ ), with





**Fig. 2** Intragroup comparisons of OSDI, TBUT, Schirmer test between day 7, day 14, and baseline (day 0) in group A. OSDI ocular surface disease index, TBUT tear-film break up time, L left eye, R right eye. \*Statistically significant difference between day 0 and day 7 ( $p < 0.05$ );

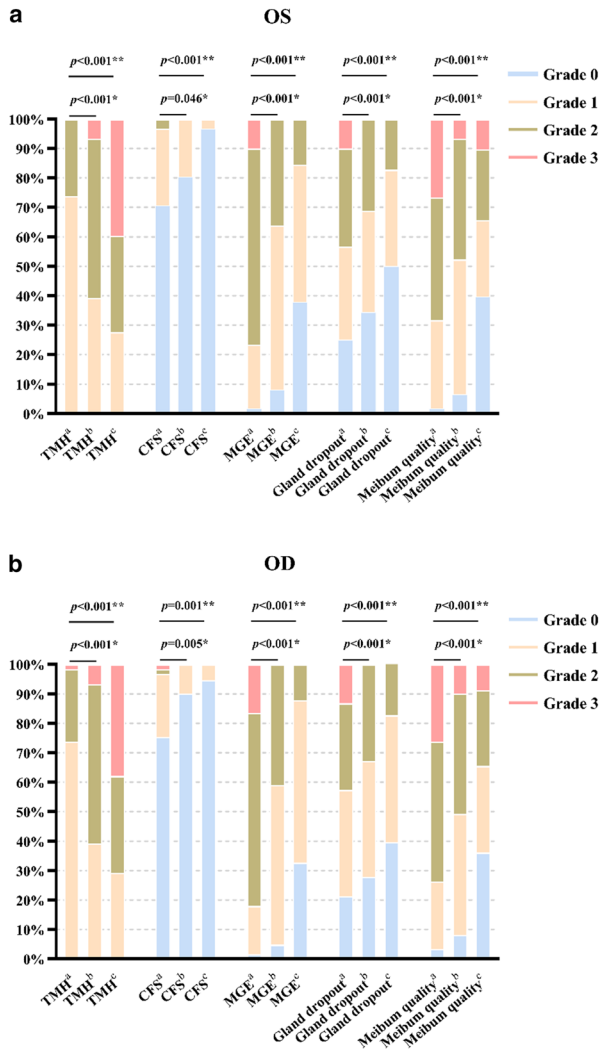
\*\*statistically significant difference between day 0 and day 14 ( $p < 0.05$ )

72.5% of left eyes and 70.7% of right eyes reaching a TMH more than 0.2 mm on day 14. Compared to baseline, the degree of CFS in both eyes significantly lightened on day 7 (L,  $p = 0.046$ ; R,  $p = 0.005$ ) and day 14 (L,  $p < 0.001$ ; R,  $p = 0.001$ ), with staining disappearing in 96.6% of left eyes and 84.8% of right eyes on day 14. Compared to baseline, the meibomian gland assessments including MGE, gland dropout, and meibum quality of both eyes all significantly improved on days 7 and 14 (all  $p < 0.001$ ). At the visit of day 14, 84.5% of left eyes and 88% of right eyes presented more than three expressible glands in the central five meibomian glands of the lower eyelid; 82.8% of left eyes and 82.8% of right eyes displayed no or less than 1/3 gland dropout; 65.6% of left eyes and 65.5% of right eyes secreted fluid meibum. Meanwhile, compared to baseline, lid margin telangiectasia of both eyes in group A was significantly ameliorated after the treatment on day 7 (L,  $p = 0.007$ ; R,  $p = 0.019$ ) and day 14 (L,  $p = 0.007$ ; R,  $p = 0.012$ ), but lid margin irregularity of both eyes in group A was only significantly ameliorated on day 14 (L,  $p = 0.001$ ; R,  $p < 0.001$ ). MGD staging of both eyes in group A was significantly improved after the treatment on day 7 (both  $p < 0.001$ ) and day 14

(both  $p < 0.001$ ), with 89.5% of left eyes and 89.4% of right eyes presenting no or only stage 1 MGD.

### Intergroup Comparison

Clinical evaluations at the endpoint were compared between two groups. As presented in Table 3, patients in group A achieved greater improvements in OSDI, TBUT, and Schirmer test at the endpoint when compared with group B. Patients in group A reported significantly lower OSDI ( $3.98 \pm 3.95$ ) than that in group B ( $5.54 \pm 5.21$ ) ( $p = 0.025$ ). Binocular TBUT in group A (L,  $7.97 \pm 4.19$  s; R,  $7.79 \pm 4.43$  s) was significantly longer than that in group B (L,  $5.14 \pm 1.99$  s; R,  $5.00 \pm 1.95$  s) (both  $p < 0.001$ ). The endpoint results of Schirmer test in group A (L,  $14.28 \pm 7.39$  mm; R,  $13.04 \pm 6.86$  mm) were significantly higher than that in group B (L,  $8.88 \pm 5.29$  mm; R,  $8.07 \pm 4.90$  mm) (both  $p = 0.007$ ). Consistently, TMH of both eyes in group A was also significantly higher than that in group B (both  $p < 0.001$ ), with 39.7% patients evaluated as 0.3 mm height in group A and only 1.6% patients assessed as 0.3 mm height in group B. However, no significant difference was observed



**Fig. 3** Intragroup comparisons of TMH, CFS, MGE, gland dropout, and meibum quality between day 7, day 14, and baseline (day 0) in group A. **a** Comparisons in left eyes in group A. **b** Comparisons in right eyes in group A. L left eye, R right eye, TMH lower tear meniscus height, CFS corneal fluorescein staining, MGE meibomian gland expressibility; <sup>a</sup>evaluated on day 0; <sup>b</sup>evaluated on day 7; <sup>c</sup>evaluated on day 14; \*statistically significant difference between day 0 and day 7 ( $p < 0.05$ ); \*\*statistically significant difference between day 0 and day 14 ( $p < 0.05$ )

in the binocular evaluation of CFS (L,  $p = 0.189$ ; R,  $p = 0.674$ ) between groups.

The comparisons of lid margin and meibomian gland assessments between groups at the endpoint are shown in Table 4. There was no significant difference in the evaluation of lid

**Table 3** Intergroup comparisons of OSDI, TBUT, Schirmer test, TMH, CFS, and MGD staging between groups A and B at endpoint (day 14)

Measurement	Group A	Group B	<i>p</i> value
OSDI	3.98 ± 3.95	5.54 ± 5.21	0.025*
TBUT, s			
L	7.97 ± 4.19	5.14 ± 1.99	< 0.001*
R	7.79 ± 4.43	5.00 ± 1.95	< 0.001*
Schirmer, mm			
L	14.28 ± 7.39	8.88 ± 5.29	0.007*
R	13.04 ± 6.86	8.07 ± 4.90	0.007*
TMH, <i>n</i> (%)			
L			
0 mm	0 (0)	0 (0)	< 0.001*
0.1 mm	16 (27.6)	40 (63.5)	
0.2 mm	19 (32.8)	22 (34.9)	
0.3 mm	23 (39.7)	1 (1.6)	
R			
0 mm	0 (0)	0 (0)	< 0.001*
0.1 mm	17 (29.3)	41 (65.1)	
0.2 mm	19 (32.8)	21 (33.3)	
0.3 mm	22 (37.9)	1 (1.6)	
CFS, <i>n</i> (%)			
L			
Grade 0	56 (96.6)	59 (93.7)	0.189
Grade 1	2 (3.4)	3 (4.8)	
Grade 2	0 (0)	1 (1.6)	
Grade 3	0 (0)	0 (0)	
R			
Grade 0	55 (94.8)	56 (88.9)	0.674
Grade 1	3 (5.2)	6 (9.5)	
Grade 2	0 (0)	1 (1.6)	
Grade 3	0 (0)	0 (0)	
MGD staging, <i>n</i> (%)			
L			

**Table 3** continued

Measurement	Group A	Group B	<i>p</i> value
Stage 0	33 (57.9)	9 (14.8)	0.019*
Stage 1	18 (31.6)	26 (42.6)	
Stage 2	4 (6.6)	20 (32.8)	
Stage 3	2 (3.3)	6 (9.8)	
Stage 4	0 (0)	0 (0)	
R			
Stage 0	30 (52.6)	8 (13.1)	0.326
Stage 1	21 (36.8)	26 (42.6)	
Stage 2	3 (5.3)	21 (34.4)	
Stage 3	3 (5.3)	6 (9.8)	
Stage 4	0 (0)	0 (0)	

*L* left eye, *R* right eye, *OSDI* ocular surface disease index, *TBUT* tear-film break up time, *TMH* tear meniscus height, *CFS* corneal fluorescein staining

\*Statistically significant between groups (*p* < 0.05)

margin telangiectasia (L, *p* = 0.990; R, *p* = 0.335) and lid margin irregularity (L, *p* = 0.193; R, *p* = 0.388) between groups. The difference of meibomian gland expressibility between groups at the endpoint was only significant in the left eye (*p* = 0.008). Similarly, the difference of gland dropout between groups at the endpoint was also only significant in the left eye (*p* = 0.018). Patients in group A showed significantly higher meibum quality than group B in both eyes (L, *p* = 0.001; R, *p* = 0.005) after the treatment. Additionally, to provide an overall assessment, group A presented significantly better MGD staging than group B in the left eye (*p* = 0.019) after the treatment (Table 3).

**Safety Evaluation**

As shown in the Supplementary Material, no significant decreased BCVA was observed in the two groups, and conversely, BCVA in both group A and group B significantly improved on

**Table 4** Intergroup comparisons of lid margin telangiectasia and irregularity, MGE, gland dropout, and meibum quality between groups A and B at endpoint

Measurement	Group A	Group B	<i>p</i> value
Lid margin telangiectasia, <i>n</i> (%)			
L	31 (53.4)	42 (66.7)	0.990
R	26 (44.8)	40 (63.5)	0.335
Lid margin irregularity, <i>n</i> (%)			
L	26 (44.8)	41 (65.1)	0.193
R	26 (44.8)	40 (63.5)	0.388
MGE, <i>n</i> (%)			
L			
Grade 0	22 (37.9)	4 (6.3)	0.008*
Grade 1	27 (46.6)	42 (66.7)	
Grade 2	9 (15.5)	17 (27.0)	
Grade 3	0 (0)	0 (0)	
R			
Grade 0	19 (32.8)	3 (4.8)	0.084
Grade 1	32 (55.2)	39 (61.9)	
Grade 2	7 (12.1)	20 (31.7)	
Grade 3	0 (0)	1 (1.6)	
Gland dropout, <i>n</i> (%)			
L			
No dropout	29 (50.0)	17 (27.0)	0.018*
< 1/3	19 (32.8)	33 (52.4)	
1/3–2/3	10 (17.2)	13 (20.6)	
> 2/3	0 (0)	0 (0)	
R			
No dropout	23 (39.7)	16 (25.4)	0.317
< 1/3	25 (43.1)	34 (54.0)	
1/3–2/3	10 (17.2)	13 (20.6)	
> 2/3	0 (0)	0 (0)	
Meibum quality, <i>n</i> (%)			
L			

**Table 4** continued

Measurement	Group A	Group B	<i>p</i> value
Grade 0	23 (39.7)	5 (7.9)	0.001*
Grade 1	15 (25.9)	22 (34.9)	
Grade 2	14 (24.1)	32 (50.8)	
Grade 3	6 (10.3)	4 (6.3)	
R			
Grade 0	21 (36.2)	5 (7.9)	0.005*
Grade 1	17 (29.3)	22 (34.9)	
Grade 2	15 (25.9)	30 (47.6)	
Grade 3	5 (8.6)	6 (9.5)	

*L* left eye, *R* right eye, *MGE* meibomian gland expressibility

\*Statistically significant between groups ( $p < 0.05$ )

day 14 after IPL treatment. In group A, one patient presented palpebral conjunctival hyperemia and discharge in the left eye on day 7, which was clinically diagnosed as bacterial conjunctivitis and recovered after conjunctival sac washing and topical administration of antibiotics. Two patients in group B were found to have a bruise to the forehead on day 7. There was no significant difference in the incidences of adverse events between two groups (1.6% vs 3.2%;  $p = 1.000$ ).

## DISCUSSION

Meibomian gland dysfunction is a highly prevalent cause of dry eye disease. The transient and unsatisfactory efficacy of conventional treatments for MGD has prompted the exploration of new therapeutic approaches, one of which is IPL treatment. In agreement with previous studies [20, 24–26, 28, 29], the results of the current non-inferiority randomized controlled trial (RCT) demonstrated the clinical efficacy and safety of a new-generation IPL device, Eysis, in the treatment of MGD-related

dry eye, and revealed its non-inferior effective rate compared with the traditional IPL device E-Eye. Subjective symptoms, tear film stability, lacrimal secretion, epithelial keratopathy, and meibomian gland function all responded positively to Eysis treatment in patients with MGD.

To the best of our knowledge, this is the first multicenter RCT comparing two different IPL devices to explore the efficacy and safety of IPL treatment for MGD. With the optimization in instrument parameters, Eysis showed more clinical benefits over E-Eye in alleviating dry eye symptoms, increasing tear film stability, stimulating tear secretion, and improving meibomian gland function in patients with MGD.

The efficacy of IPL in the treatment of MGD mainly depends on the wavelength, pulse width, pulse number, and energy intensity of high-intensity light emitted from the device, parameters which have been optimized in the design of the new-generation IPL device to obtain better efficacy and safety. The range of energy intensity in the Eysis device has been expanded from 5 to 15 J/cm<sup>2</sup>, and divided into 21 grading levels based on both skin phenotype and MGD severity. As a consequence, Eysis IPL treatment is more personalized and precisely targeted. Moreover, the number of pulses has been increased to 10 pulses per cluster so that more energy can be effectively transferred to the meibomian gland to improve its function. Last but not least, in the Eysis device, the light pulses are delivered in the shape of “smile”, which ensures the continuous cycle of “skin preheating, energy injection, heat preservation, repeated injection, warm exiting” as illustrated in the Supplementary Material and thus contributes to the deeper penetration of energy in the meibomian glands. Meanwhile, the reduced loss of energy in the skin and subcutaneous tissue could result in a higher efficiency of treatment and lower risk of thermal damage in the treatment area.

The alterations of meibomian gland expressibility and meibum quality play a core role in the progression of MGD. Our study revealed that IPL treatment could significantly improve the quality and expressibility of meibum, which is in accordance with previous studies [20, 24–26, 28, 29]. It has been proposed

that eyelid temperature greatly influences the physical properties of meibomian gland secretions [40]. The thermal energy transferred by IPL therapy is thought to melt and liquefy the viscous meibum in MGD, remove ductal obstruction, and encourage the release of meibomian lipids into the tear film [41]. Moreover, compared with the traditional E-Eye device, Eysis showed clinical benefits in improving meibomian gland expressibility and meibum quality according to our results, improvements which might be due to the optimization of pulse number and intensity grading. The number of pulses in Eysis increases to 10 pulses per cluster so that more energy could be effectively transferred to the meibomian glands to heat the meibum and promote the expressibility. Meanwhile, the new grading system of energy intensity in Eysis that combines meibum quality with skin color together is more precise and severity-targeted, especially for those who suffer critical MGD but present light skin. Additionally, apart from the heat effect, the reduction of bacteria and parasitic growth on the eyelids and eyelashes might be another potential mechanism of IPL treatment. *Demodex folliculorum* and its commensal bacteria *Bacillus oleronius* could release toxic substances that could increase meibum viscosity and promote orifice obstruction, which together contribute to the blepharitis and MGD [42–44]. Histological analysis confirmed that IPL could induce the coagulation and necrosis of *D. folliculorum* thanks to the presence of chromophore in its pigmented exoskeleton [45].

In addition to the improvement of meibum secretion, IPL therapy also appears to play a positive role in ameliorating the structure of meibomian glands and lid margin. In our research, gland dropout and lid margin irregularity were both remarkably improved after IPL treatment. In patients with MGD, plugging ducts is accompanied by elevated intraductal pressure and intraglandular cystic dilation, leading to disuse or pressure atrophy of the glands which appears as gland dropout on meibography [1, 6]. Yin et al. revealed that IPL treatment could evidently improve the meibomian gland microstructure including the acinar longest diameter and acinar unit density [30]. It

has been speculated that these microstructure improvements of meibomian glands are induced by the photomodulation effect of IPL [12]. IPL activates a photochemical cascade and the reactions along the mitochondrial respiratory chain, leading to faster electron transfer and increased adenosine triphosphate (ATP) production [46, 47]. The rise of ATP results in higher levels of intracellular free calcium that could stimulate acinar cell activity, promote fibroblast proliferation, enhance collagen synthesis, and increase local blood flow, thus improving meibomian glands structure [46, 47]. On the basis of our results, Eysis was more effective than E-Eye in improving the gland dropout. Therefore, considering the better benefits of Eysis on the structure of meibomian glands, for patients with severe terminal stage MGD which is known to present structural abnormalities and be refractory to traditional therapies [23], we suggest that Eysis could be a promising better treatment modality. Similarly, lid margin irregularity, which is thought to be the irreversible result of meibomian gland dropout, was also improved in our study. Consequently, better apposition of the lid margin and more complete blinks occurred to increase meibum pumping.

Schirmer test and tear meniscus height have been adopted as common methods for clinical evaluation of tear secretion, providing an index of lacrimal gland function. It is traditionally believed that IPL therapy mainly improves the function of meibomian glands and exerts little impact on lacrimal gland function. Surprisingly, our study found that Schirmer test and TMH both dramatically improved after Eysis IPL treatment, which was not detected in the E-Eye treatment group and contradictory to previous studies [20, 27, 28]. In fact, no research has been conducted specifically to explore the impact of IPL on the function of lacrimal gland yet, whereas there are several reports on the occurrence of enhanced sweat gland secretion and hyperhidrosis with skin laser treatment [48–50]. Aydin et al. found increased axillary sweating after hair removal by 1064-nm laser, and they proposed that the deep penetration of the laser could stimulate the nerve fibers that innervate sweat glands by direct thermal heating or



inducing sympathetic skin response [48]. Therefore, we speculated that the optimized continuous “smile” mode of IPL in the Eysis device enabled the deeper penetration of energy, and thus stimulated the accessory lacrimal glands or the palpebral lacrimal gland to promote aqueous secretion by thermal effect or sympathetic response. Another possible explanation for the increased aqueous volume after Eysis treatment is the recovery of reflected lacrimal secretion. In MGD-related dry eye with normal lacrimal function, tear volume and meniscus dimensions can be sustained or even increased by a compensatory response driven by the reflection of lacrimal functional unit [51, 52]. However, in severe MGD, reduced corneal sensitivity could remove the compensatory lacrimal secretion and lead to a secondary aqueous deficiency [6]. The substantial improvements of ocular surface environment after Eysis IPL treatment may restore the damaged cornea nerves and enhance corneal sensitivity, thereby recovering the compensatory tear production.

The functional alterations in meibomian glands contribute to an overevaporated and unstable tear film, resulting in a shortened TBUT. Our study found that TBUT was significantly lengthened after Eysis treatment, which implied that Eysis could stabilize the tear film effectively. The result is consistent with other traditional IPL devices [20, 22–26]. The tear film is a highly organized structure on the ocular surface; its stability and function are strongly dependent on its biochemical composition [53]. The improved function of meibomian glands and enhanced lacrimal secretion by Eysis IPL treatment may have a direct effect on the stability of tear film. According to a consensus reported by the Asia Dry Eye Society, a cutoff value of 5 s has been applied as the diagnostic criteria of dry eye [54]. We found that Eysis treatment could lengthen binocular short TBUT to more than 7 s, representing a meaningful clinical improvement in addition to a statistically significant improvement. However, the conventional IPL treatment in our study cannot achieve this goal, indicating the superiority of the Eysis device over the E-Eye device in improving tear film stability. Meanwhile, the

TBUT after IPL treatment in our study still did not achieve the normal level (10 s), suggesting the need for increasing treatment sessions and prolonging treatment duration.

Ocular surface damage is regarded as a terminal event in the pathological process of MGD-related dry eye, which could be detected by corneal fluorescein staining [6]. Consistent with previous studies [25, 26, 28, 29], CFS was significantly alleviated after IPL treatment in our study, with more than 90% of patients presenting no staining. The anti-inflammatory action of IPL therapy might be the key mechanism in restoring cornea damage. During IPL treatment, light energy absorbed by chromophores is transformed into heat causing the coagulation and closure of superficial blood vessels, thus eliminating the lid margin telangiectasia and removing a major source of inflammation on the ocular surface [55]. Choi et al. concluded that IPL significantly reduced inflammatory markers in tears of patients suffering MGD-related DED, including interleukin (IL)-6, IL-10, IL-17A, and tumor necrosis factor alpha (TNF $\alpha$ ) [22], and Liu et al. demonstrated that the changed level of cytokines in tears after IPL treatment was correlated with that of CFS [21]. Therefore, the downregulated inflammation on the ocular surface after IPL could reduce the damage to the corneal epithelium and provided a stable environment for its restoration.

In addition, the improvement in clinical evaluation was accompanied by attenuation in self-reported symptoms covered by the OSDI questionnaire, similar to the results of previous studies [20, 24–26, 28, 29]. Diminished inflammation was associated with the relief of eye irritation and foreign body sensation, and lengthened TBUT could help improve the symptoms of dryness and blurred vision.

As shown in the Supplementary Material, no significant decreased BCVA was observed in both treatment groups. Conversely, it was noteworthy that BCVA significantly improved after IPL treatment in the two groups, which might be the result of ameliorated blurred vision by lengthened TBUT. The ocular examination revealed that one patient in the Eysis treatment group developed bacterial conjunctivitis in the left eye on day 7 which was

considered unrelated to IPL treatment. The periocular skin evaluation indicated that two patients in the E-Eye treatment group had a bruise on the forehead on day 7 which was thought to result from the thermal effect of IPL therapy. However, no bruise or redness event was observed in the Eysis group. On the one hand, the grading strategy of energy intensity of Eysis combined the severity of MGD and skin color together, which could be more personalized and avoid excessive energy, especially for those who presented dark skin but only suffered mild MGD. On the other hand, the continuous “smile” pulses of Eysis substantially reduced the energy loss in the skin layer and decreased harmful heat cumulation. Therefore, we propose that the optimized Eysis could be a safer IPL device with lower risk of thermal damage in periocular skin.

As a new-generation IPL device, Eysis showed more clinical benefits compared to E-Eye in improving meibomian gland function, including meibomian gland expressibility, gland dropout, and meibum quality. Compared with the traditional IPL device, the optimizations of Eysis are mainly concentrated on three aspects. Firstly, the range of energy intensity has been expanded, and the grading strategy of energy becomes grounded on the severity of MGD. The more precise treatment ensures adequate energy to be effective and avoid excessive energy to do harm. Secondly, the number of pulses has been increased to 10 pulses per cluster to make sure that more energy could be effectively transferred to the meibomian gland. Thirdly, in the Eysis device, the light pulses are continuously emitted by the regulated “smile” mode to promote deeper penetration of energy and reduce energy loss in the superficial tissue, making a higher treatment efficiency and lower thermal damage risk possible. Additionally, we observed dramatically improved tear volume after Eysis IPL treatment, which was not found in E-Eye or any other IPL devices before. We propose that the deeper penetration of energy in Eysis could stimulate the secretion of accessory lacrimal glands or palpebral lacrimal gland by thermal effect or sympathetic response. The improvements of lacrimal secretion and meibomian gland function

contributed to a more stable ocular surface environment, thereby restoring the damaged cornea nerves and ultimately enhancing the compensatory tear production.

There are several limitations in our study. First, Eysis is a newly designed IPL treatment device, and its safety has not been completely proved before. Therefore, considering its uncertain safety, we reduced the treatment times and shortened the treatment interval so that any adverse events could be revealed and we could intervene in time. Consequently, the short time of observation was limited to 14 days, which may fail to capture the long-term cumulative result and changing trend of treatment effects. Studies with a longer follow-up period and crossover design are needed in the future. Second, the treatment effect of IPL may correlate with the severity of MGD-related dry eye. Subgroup analysis based on the severity and stage of MGD is lacking. Finally, mechanisms of IPL treatment in MGD eyes were not proven in our study. Further evaluations, including inflammatory cytokine examination, eyelid microbiology culture, and microstructure observation of meibomian glands, should be conducted to figure out the potential mechanisms of IPL therapy.

## CONCLUSION

Our study concluded that the new-generation IPL device Eysis was effective and safe in relieving the symptoms and signs of MGD-related dry eye. The Eysis IPL device exhibited non-inferior effective rate in treating MGD-related dry eye compared to the traditional IPL device E-Eye. Additionally, Eysis showed more clinical benefits over E-Eye in alleviating dry eye symptoms, increasing tear film stability, stimulating tear secretion, and improving meibomian glands function among patients with MGD-related dry eye.

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**Compliance with Ethics Guidelines.** This trial adhered to the tenets of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of Peking University Third Hospital and Wangjing Hospital of Chinese Academy of Traditional Chinese Medicine.

**Data Availability.** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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