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Jennifer P. Craig, Alex Muntz, Michael TM. Wang, Doerte Luensmann, Jacqueline Tan, Sonia Trave Huarte, Ally L. Xue, Lyndon Jones, Mark Dp Willcox, James S. Wolffsohn

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Manuscript title: Developing evidence-based guidance for the treatment of dry eye disease with artificial tear supplements: a six-month multicentre, double-masked randomised controlled trial

Short title: Evidence-based guidance for treating dry eye disease

Authors:

Jennifer P Craig PhD FCOptom [1, 2, 4]
Alex Muntz PhD [1]
Michael TM Wang MBChB [1]
Doerte Luensmann OD PhD [2]
Jacqueline Tan PhD BScOptom [3]
Sonia Trave Huarte BSc [4]
Ally L Xue PhD BOptom [1]
Lyndon Jones PhD FCOptom [2, 5]
Mark DP Willcox PhD [3]
James S Wolffsohn PhD FCOptom [4]

Author institutions:

1 Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, New Zealand
2 Centre for Ocular Research & Education (CORE), School of Optometry and Vision Science, University of Waterloo, Canada
3 School of Optometry and Vision Science, University of New South Wales, Sydney, Australia
4 Optometry and Vision Science Research Group, Aston University, Birmingham, UK
5 Centre for Eye & Vision Research (CEVR), Hong Kong

Corresponding author:

Associate Professor Jennifer P Craig
Department of Ophthalmology
New Zealand National Eye Centre
The University of Auckland
Private Bag 92019
Auckland 1142
New Zealand

Phone: +64 9 923 8173
Fax: +64 9 367 7173
Email: jp.craig@auckland.ac.nz

ABSTRACT

Purpose: To assess the six-month therapeutic profiles of lipid and non-lipid-based artificial tear supplements in managing dry eye disease (DED).

Methods: Ninety-nine participants fulfilling the TFOS DEWS II diagnostic criteria for DED (64% females; mean±SD age, 44±16 years) were enrolled in a prospective, multicentre, double-masked, parallel group, randomised controlled trial. Participants instilled lipid-based nano-emulsion drops or non-lipid-based aqueous drops for six months at least four times daily. Symptomology, tear film and ocular surface characteristics were assessed at Days 0, 30, 60, 90, 120, 150 and 180.

Results: Sustained reductions in OSDI, DEQ-5, and SANDE symptom scores from baseline were observed from Day 30 onwards in both groups (all $p<0.05$) and decreased superior lid wiper epitheliopathy grades from Day 60 onwards (all $p\leq0.01$). Improvements in non-invasive tear film breakup time, sodium fluorescein and lissamine green staining scores followed from Day 120 onwards in both groups (all $p<0.05$). Tear lipid layer grades increased from Day 90 onwards only with the lipid-based drops, and with significantly greater improvement in those with suboptimal lipid thickness at baseline (grade ≤3; $p=0.02$). By Day 180, 19% of participants no longer fulfilled the DED diagnostic criteria.

Conclusions: Over six-months treatment, improvements in dry eye symptomology preceded tear film and ocular surface changes with both lipid and non-lipid-based artificial tear supplements. Both formulations addressed most mild-to-moderate forms of aqueous and evaporative DED, while evaporative cases benefitted preferentially from lipid-based supplementation. This represents a first step towards mapping DED therapeutic strategies according to disease subtype and severity.

KEYWORDS

Dry eye disease; meibomian gland dysfunction; artificial tear supplement; lipomimetic; aqueous deficiency; evaporative

INTRODUCTION

Topical eye drops that supplement the natural tear film are the mainstay therapy for dry eye disease (DED). [1] The recent focus on meibomian gland dysfunction and lipid deficiency has driven a substantial evolution of artificial tear supplement formulations. While still presenting a largely palliative solution to managing dry eye, lipid components have been incorporated to address tear lipid deficiency, and aqueous based supplementation continues to be used to target lacrimal insufficiency. However, practitioners seeking guidance in their choice of artificial tear supplements for the treatment of dry eye disease are faced with a dearth of sound scientific evidence, as comparative efficacy studies on lipid and non-lipid formulations across the breadth of dry eye subtypes are limited and the quality of evidence is generally low. [2–8] The need for more robust, level 1 comparative efficacy randomised controlled trials (RCTs) for lipid and non-lipid-based formulations to guide the targeted treatment according to individual presenting patient characteristics, dry eye subclassification and severity is widely acknowledged. [1,6,9]

Another area important to clinicians and their patients, but which is similarly devoid of sufficient attention in the literature, is the temporal profile or clinical course of artificial tear supplement efficacy. In a Cochrane review of 43 RCTs on artificial tear solution use for the treatment of DED, [6] the average study follow-up duration was six weeks; three trials featured a three-month follow-up and only a single study attempted to investigate drop use over 12 months. [10] Many studies focus on the immediate or short-term effects of a single instillation. Longer-term efficacy studies that more closely resemble intended clinical use are necessary to inform clinicians and patients about the recommended length of treatment regimes. An evidence-based approach may assist practitioners in encouraging patient compliance by setting realistic expectations on the time course of clinically significant improvements in signs and symptoms, and around the anticipated maximal treatment effect.

The objectives of this six-month, international multi-centre, double-blind, randomised controlled trial on dry eye disease, diagnosed using global consensus criteria, [11] were to:

1) compare the efficacy of a lipid and a non-lipid based artificial tear supplements for the management of DED; 2) determine the temporal-therapeutic profile for clinically significant improvements of signs and symptoms, including the magnitude of change and the time taken before maximal clinical benefit was observed; and 3) assess whether clinical outcomes were influenced by baseline dry eye disease subtype or severity. [9,11]

MATERIALS AND METHODS

2.1. Subjects

This prospective, multicentre, randomised, double masked, parallel group, 6-month efficacy trial adhered to the tenets of the Declaration of Helsinki and was approved by the Universities of Auckland, Aston, New South Wales and Waterloo Human Participants Ethics Committees. The study was registered as a clinical trial (ACTRN12619000390189) and abided by the CONSORT statement (Figure 1). [12] The study was conducted between March 2019 and March 2020 at clinical academic sites in Australia, Canada, New Zealand and the UK. Participants were required to be 18 years or older, with manifest symptoms and signs of dry eye disease according to the TFOS DEWS II diagnostic criteria (Ocular Surface Disease Index (OSDI) score ≥13 or 5-Item Dry Eye Questionnaire (DEQ-5) ≥6, with at least one positive indicator of homeostatic imbalance based on non-invasive tear film break up time (NIBUT), tear osmolarity and/or ocular surface staining). [11] In addition, participants were required to be non-contact lens wearers; not be pregnant or planning to become pregnant in the next 12 months; to self-report having experienced dry eye symptoms for a minimum of six months; report no history of major systemic or ocular conditions; report no ophthalmic surgery in the previous three months or during the treatment period; report no use of systemic or topical medications known to affect the eye two weeks prior to baseline assessment or during the treatment period. Therapeutic measures were allowed during the study period, however, no changes to any treatment courses or routines (such as warm compresses) were permitted during the study. Eligible participants were enrolled for baseline screening after providing written informed consent to participate.

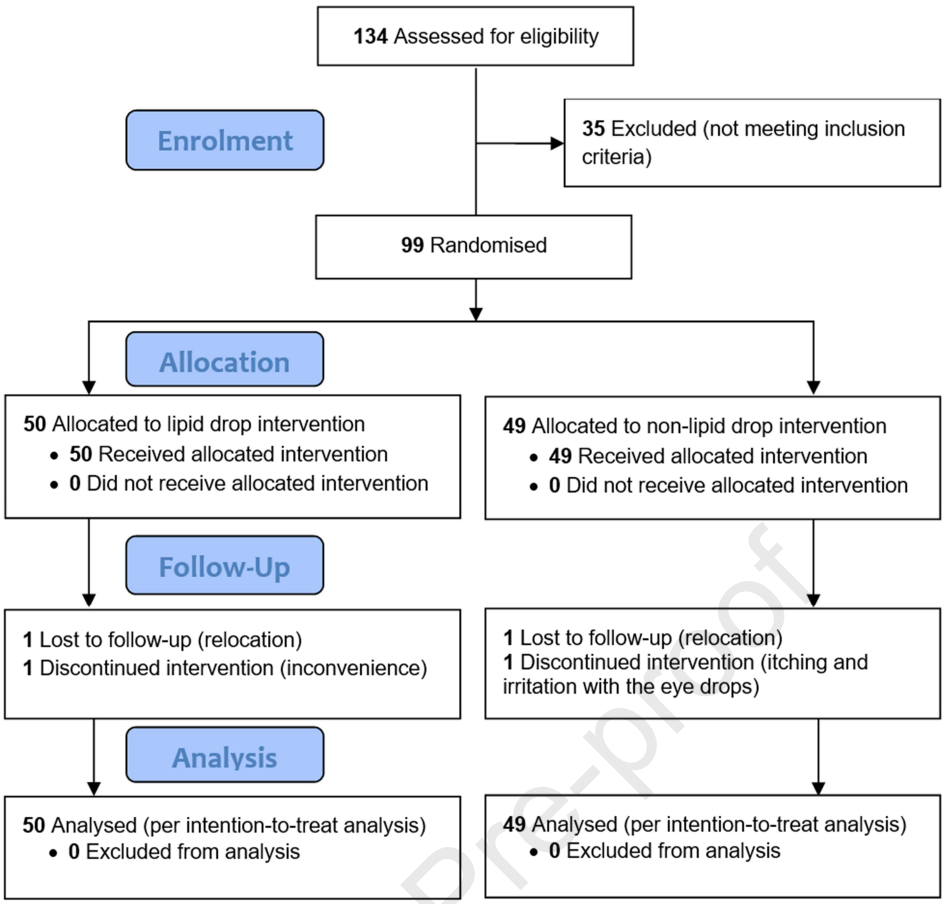

Figure 1: Consolidated Standards of Reporting Trials 2010 Flow Diagram

A total of 99 eligible participants were recruited, exceeding the minimum sample size requirements for the desired study power. Sample size was determined from non-parametric adjusted power calculations conducted using PASS 2002 (NCSS, Kaysville, UT), with NIBUT and OSDI as the designated primary outcome measures, using a NIBUT standard deviation estimate of 6 seconds.[13] The power calculation showed that a total of 84 participants with a minimum of 42 participants per treatment group, was required to allow detection of a clinically significant difference of 4 seconds, with 80% power ($\beta = 0.2$), at a two-sided statistical significance level of 5% ($\alpha = 0.05$).

2.2. Interventions

The study compared an aqueous-based drop and a combination lipid-aqueous nanoemulsion. The aqueous-based drop (Systane Ultra, Alcon, Fort Worth, TX, USA)

contains aminomethylpropanol, boric acid, hydroxypropyl guar, POLYQUAD (polyquaternium-1) 0.001% preservative, sorbitol; the lipid-aqueous drop (Systane Complete, Alcon, Fort Worth, TX, USA) contains boric acid, dimyristoyl phosphatidylglycerol, edatate disodium, hydroxypropyl guar, mineral oil, polyoxl 40 stearate, POLYQUAD 0.001% preservative, sorbitan tristearate, sorbitol.

Participants were randomised to four times (minimum) daily topical application of either the non-lipid drop (n=49 in total) or the lipid drop (n=50 in total) in both eyes for a 6-month period. Randomisation was conducted by computer-generated random number allocation and applied to sequentially enrolled participants. The randomisation schedule was determined prior to participant recruitment, such that the investigator involved in baseline participant assessment had no involvement in treatment allocation. Product labels were removed, and customised labels applied to obscure contents. Hence, the study was double masked. Outcome measures were evaluated at 30, 60, 90, 120, 150 and 180 days after the baseline visit. Returned eyedrop bottles were weighed at each visit to determine patient compliance. Treatment success at six-months was judged as an improvement of > 4s in NIBUT and/or a ≥4.5 point reduction in OSDI symptom score. [13,14] Participants were instructed to avoid eye drop instillation for at least 90 minutes prior to measurements being collected at review appointments. Any other treatments (such as warm compresses or lid hygiene) were not permitted on the day of testing.

2.3. Measurements

Participants were assessed at one of four sites, with room temperature of 21.5 ± 1.5 °C and relative humidity of 47.8 ± 11.3 % (mean ± SD). Ocular measurements were conducted on the right eye only of each participant (except for osmolarity where the manufacturers recommendations require both eyes to be assessed). Clinical tests were administered in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology

subcommittee. [11] To reduce the impact on tear film physiology, the tests were ordered from least to most invasive at each study visit (Table 1).

Ocular comfort was assessed using the OSDI, DEQ-5, and the Symptom Assessment in Dry Eye (SANDE) questionnaires during the treatment period. [15] The overall SANDE score was calculated as the geometric mean of the frequency and severity scores. [16] Participants were advised to contact the study investigators during the study period to report adverse events at any time.

Blinking frequency, bulbar conjunctival hyperaemia, tear meniscus height, NIBUT, and lipid layer grade (LLG) were assessed using the Keratograph 5M (Oculus Optikgeräte, Wetzlar, Germany). Blinking frequency was determined by visual counts from videos recorded using infrared illumination of naïve participants. Bulbar conjunctival hyperaemia was evaluated by automated objective evaluation of high magnification digital imaging, benchmarked against the JENVIS grading scale from 0 to 4.[17] The lower tear meniscus height was assessed using high magnification pre-calibrated digital imaging, and three measurements within 1mm of pupil centre at the lower meniscus were averaged. NIBUT was measured using automated detection of first break-up, while the subject maintained fixation and was requested to refrain from blinking. Three breakup time readings were averaged in each case. [11] Tear film lipid layer interferometry was graded by a single researcher across all participants according to the modified Guillon-Keeler system: grade 1, open meshwork; grade 2, closed meshwork; grade 3, wave or flow; grade 4, amorphous; grade 5, coloured fringes; grade 0, non-continuous layer (non-visible or abnormal coloured fringes). [18,19]

Tear film osmolarity measurements were performed with a clinical osmometer (TearLab, Escondido, CA), from 50nL tear samples collected from the lower lateral canthus tear meniscus. A measurement was taken for each eye, and the higher reading and the inter-ocular difference recorded. [11]

Lid margin and eyelash abnormalities, including lid margin thickening, rounding, notching, foaming, telangiectasia, meibomian gland capping, staphylococcal lash crusting, seborrhoeic

lash crusting, and *Demodex* blepharitis based on eyelash cylindrical dandruff were assessed by slit lamp biomicroscopy examination. [20] Grading of the clinical features was based on a four-point scale: grade 0, absent; grade 1, mild; grade 2, moderate; grade 3, severe. [17]

Sodium fluorescein (Fluorets, Laboratoire Chauvin, France) and, where pharmaceutical regulations permit, lissamine green dyes (Green Glo, HUB Pharmaceuticals, Rancho Cucamonga, CA) were applied using previously recommended techniques, [11] in order to evaluate localised corneal and conjunctival areas of epithelial desiccations. Staining was recorded using the modified Oxford grading scheme, [21] and lid wiper epitheliopathy (LWE) was evaluated relative to Korb's grading. [22]

Meibum expressibility of the inferior eyelid meibomian glands was assessed using the Meibomian Gland Evaluator (TearScience/Johnson & Johnson, Morrisville, NC, USA), with a standardised pressure of 1.2g/mm^2 applied just inferior to the nasal, central, and temporal aspects of the eyelid margin. The number of meibomian orifices yielding lipid secretions was graded on a five-point scale: 0, more than 75%; 1, 50% to 75%; 2, 25% to 50%; 3, less than 25%; 4, none. The quality of expressed meibum was graded according to appearance, as: grade 0, clear; grade 1, cloudy; grade 2, cloudy with debris (granular); grade 3, thick, toothpaste-like; grade 4, waxy, inexpressible. [23] Infrared meibography was performed with the Oculus Keratograph 5M, whereby the superior and inferior eyelids were everted and imaged in turn. From the captured images, the proportion of meibomian glands visible within the tarsal area was graded by a single researcher across all participants according to the five-point Meiboscale. [24]

Best spectacle corrected visual acuity was recorded as a safety measure at each visit on a six-metre logMAR chart.

2.4. Statistics

Statistical analysis was conducted with Graph Pad Prism version 8.01 (GraphPad Software, San Diego, CA) and SPSS version 24 (IBM, New York, NY). Primary outcomes were NIBUT, and OSDI score. Intention-to-treat analysis was conducted using the last observation carried forward method. Mixed-effects model two-way analysis of variance (ANOVA) testing was conducted to examine the significance of treatment, time and interaction (treatment-by-time) effects on measurements over the six-month period, where continuous variables with a normal distribution had been confirmed (Shapiro-Wilk test $p>0.05$). Non-normally distributed continuous measures were logarithmically transformed prior to undergoing analysis. Post-hoc analysis for the significance of treatment effects at each time point, and intra-group comparisons relative to baseline, was conducted using the multiplicity adjusted Sidak's test. Analysis of ordinal data was performed using multiple ordinal regression, with post-hoc analysis of treatment effects at each time point conducted using the multiplicity-adjusted non-parametric Dunn's test. Categorical data at baseline were analysed using chi-squared or Fisher's exact tests. All tests were two-tailed, and $p<0.05$ was considered significant. Data are presented as mean±SD, or median (IQR) unless otherwise stated.

RESULTS

A total of 95 participants (64 females and 31 males) with a mean ± SD age of 44 ± 16 years (range, 21 to 75 years), completed the study. Four participants discontinued participation over the course of the study, however, analysis was conducted for n=99, according to the intention-to-treat analysis (Figure 1).

Demographic characteristics of the participants are summarised in Table 2, and clinical measurements during the six-month study period are presented in Table 3 and Supplementary Tables 1 to 3. Baseline characteristics did not differ between treatment groups (all p>0.30). Returned eye drop bottles at each visit averaged a weight reduction of 6.6 ± 3.4 grams between study groups (p=0.71), equating to the application of approximately four drops daily, indicating good product administration adherence.

All participants fulfilled the TFOS DEWS II criteria for dry eye disease at baseline; by the end of the study, 19% of all participants no longer fulfilled these criteria (Figure 2, Supplementary Table 1).

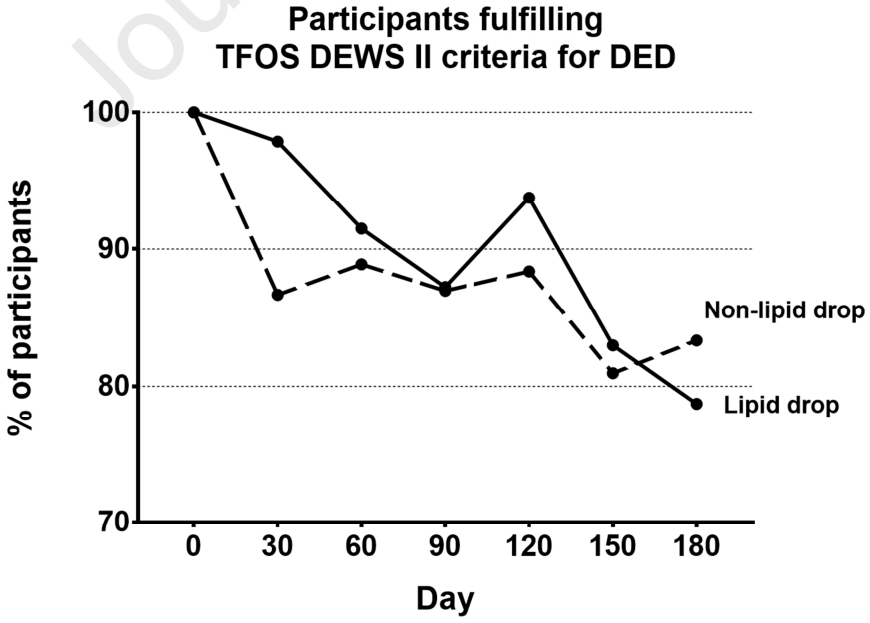

Figure 2: Recovery of DED status according to TFOS DEWS II criteria [11] in the lipid and non-lipid groups at each study visit.

Participants showing an improvement from baseline of > 4s in NIBUT and/or a ≥ 4.5-point reduction in OSDI were classified as 'responders' to treatment. [13,14] At Day 30, 69.5% and by Day 180, 74.2% of all participants responded to treatment, with no difference between treatments. Throughout the study period, responders showed an average improvement of 16.6 ± 12.8 in OSDI symptomology score and of 4.5 ± 5.6 seconds in NIBUT. Non-responders, however, registered an overall worsening of -2.4 ± 10.5 in OSDI and of -0.5 ± 3.7 seconds in NIBUT.

3.1. Visual acuity and adverse events

There were no significant treatment, time, or treatment-by-time interaction effects for best-corrected visual acuity (all p>0.40, Table 3). Two non-significant adverse events deemed unrelated to the study drops (conjunctivitis) and one drop-related non-significant adverse event (reported itching and irritation following drop application) occurred during the study. All events resolved without sequelae or additional treatment between three and seven days after onset.

3.2. Dry eye symptomology

Mixed-effects model ANOVA demonstrated significant time effects for OSDI, DEQ-5, and SANDE dry eye symptomology scores (all p<0.001, Table 3), although treatment and interaction effects were non-significant (all p>0.20, Table 3). Multiplicity-adjusted post-hoc testing demonstrated sustained reductions in OSDI, DEQ-5, and SANDE scores from Day 30 onwards in both treatment groups (all p≤0.01, Supplementary Table 3, Figure 3).

3.3. Tear film quality and quantity

A significant time effect was detected for NIBUT (p<0.001, Table 3), although treatment and interaction effects were non-significant (both p>0.60, Table 3). Multiplicity-adjusted post-hoc

analysis demonstrated sustained improvements in tear film stability from Day 120 onwards in both treatment groups (all $p<0.05$, Supplementary Table 3, Figure 3).

Treatment and interaction effects were significant for tear film lipid layer grade (both $p\leq0.01$, Table 3). Multiplicity-adjusted post-hoc testing demonstrated that improvements in tear film lipid layer quality from Day 90 onwards were limited to the lipid-based tear supplement group (all $p<0.05$, Supplementary Table 3), with measurements being greater than the non-lipid containing eye drop group (all $p<0.05$, Supplementary Table 2, Figure 3). Subgroup analysis demonstrated significant inter-treatment differences in the maximal change of tear film lipid layer grade during the study period were limited to participants with a baseline grade of 3 or less (median change of +1 versus 0 grades, $p=0.01$).

Treatment, time, and interaction effects for tear meniscus height and tear osmolarity were not statistically significant (all $p>0.30$, Table 3).

3.4. Ocular surface characteristics

Time effects were significant for superior lid wiper epitheliopathy grade, and sodium fluorescein and lissamine green staining scores (all $p<0.01$, Table 3). Multiplicity-adjusted post-hoc analysis demonstrated significant decreases in superior lid wiper epitheliopathy grade in both treatment groups from Day 60 onwards (all $p\leq0.01$, Supplementary Table 3, Figure 3), and improvements in sodium fluorescein and lissamine green staining scores from Day 120 onwards (all $p<0.05$, Supplementary Table 3, Figure 3). No significant treatment, time, or interaction effects were detected for conjunctival hyperaemia, inferior lid wiper epitheliopathy, eyelid margin and eyelash characteristics, meibomian gland dropout, and meibum expressibility and quality (all $p>0.05$, Table 3).

3.5. Blinking assessment

Treatment, time, and interaction effects for blink rate and the proportion of incomplete blinks were not statistically significant (all $p>0.10$, Table 3).

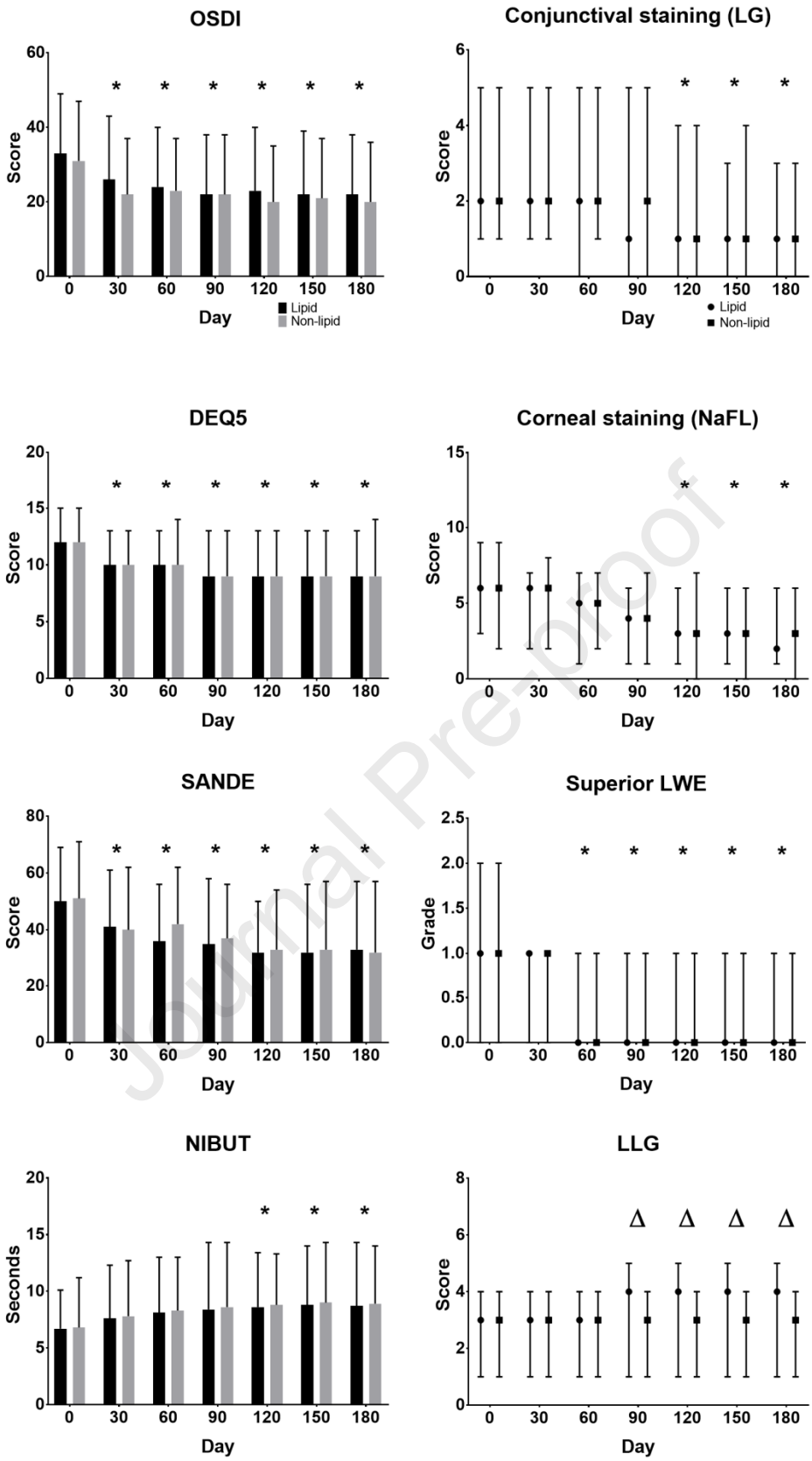

Figure 3: Clinical measurements of participants randomised to lipid and non-lipid-containing eye drops showing statistically significant improvements at the indicated timepoint relative to baseline. Asterisks denote significant changes observed for both drops, and triangle symbols signify significant changes observed for the lipid-containing drop only. Symptomology and NIBUT data are presented as mean±SD, and LLG and epithelial staining as medians and IQR.

DISCUSSION

This study provides level 1 clinical evidence for the long-term efficacy of lipid and non-lipid ocular lubricants for the management of dry eye disease. Both formulations demonstrated similar performance, with the exception of tear lipid layer grade improvements, which were limited to the lipid-based drop, from Day 90 onward. This relatively late onset, but sustained change in lipid layer grade thereafter suggests that there may be more than a simple transient effect at play. The mechanism underlying this phenomenon is unclear, but the slow fortification of the lipid layer through daily, sustained, repeated lipid supplementation seems to be affecting the ocular surface physiology which in turn restores tear film homeostasis. The tear film stability that improved after four months of drop use may serve to reduce the level of subclinical inflammation secondary to a loss of tear film homeostasis, helping to break the vicious cycle of dry eye disease and promote improved meibomian gland function. [25,26] The possibility that long-term lipid supplementation may be linked to improved meibomian gland function warrants future exploration and lends pragmatic support for the prolonged rather than sporadic clinical application of artificial tear supplements.

A study comparing the same proprietary lipid-aqueous-based to aqueous-based supplements reported that short-term changes in objectively determined lipid layer thickness were limited to the lipid-aqueous nanoemulsion. However, no effects were observed 15 minutes post-instillation, or after a month of four times daily instillation.[27] Other studies have also failed to detect differences in lipid layer thickness minutes to days post-instillation of these or other lipid-based drops.[28–30] Reasons for differences might relate to the nature of subjective lipid layer grading which reflects the dynamic distribution profile of the entire interpalpebral lipid layer, [31] rather than an average of absolute measures of lipid thickness calculated over a predefined area. In the present study, improvements in tear film lipid layer grades were exclusively associated with the nanoemulsion and in participants with poor baseline lipid status. Similarly, in another recent study, lipid layer deficient individuals showed a subjective preference for a liposomal spray. [32] However, the 6-month rather than 1-month follow up of this study has further allowed exploration of longer-term effects and

provided evidence to support recommending lipid-based products for patients identified with tear lipid deficiency.

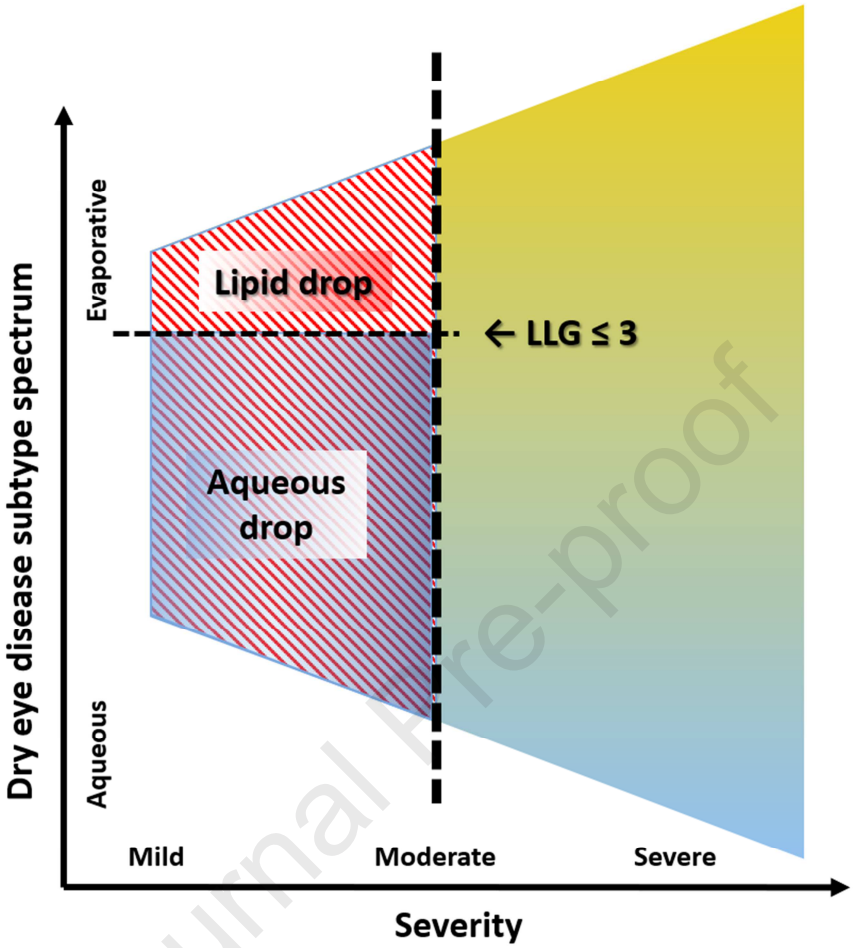

Figure 4: Schematic representation of the differential suitability of lipid and non-lipid drop formulations by DED subtype and severity. [11] Mild to moderate aqueous deficient and evaporative cases respond well to both formulations; however, subgroup analysis demonstrated that participants with predominantly evaporative dry eye disease due to lipid insufficiency (with an LLG ≤ 3 in this study cohort) preferentially benefit from lipid-based supplementation. Study cohort did not include moderate-severe cases.

Drop efficacy demonstrated a distinct time course for the onset of each of the clinical benefits. Relatively rapid and then sustained symptomatic relief occurred at the first month of use with both drops, which is consistent with the outcomes of previous studies with shorter follow up periods.[2,7,8,27,33] In the current study, symptomatic improvement plateaued after Day 30 and at the 6-month time point, both drops demonstrated statistically and clinically significant symptomatic improvements averaging a reduction of 11, 3- and 17-

points in OSDI, DEQ-5 and SANDE scores, respectively. The relatively early onset of superior LWE improvements observed with both drops, which suggests reduced blink-related friction at the lid wiper, aligns favourably with the symptomatic improvement. Effects on the upper eyelid only may reflect the extended travel of the upper compared to the lower lid during the blink. [34] Further research is warranted to determine whether the relatively late onset of lipid layer thickness and ocular surface staining and purported glandular function improvements may lead to further symptomatic improvement beyond the time course of the present study. [11]

Improvements in tear film stability and ocular surface integrity were more gradual than symptomatic improvements and became detectable after three to four months of regular drop use. This relatively late onset suggests, similarly to the observed effects with the lipid layer, that restoration of the ocular surface requires prolonged and regular tear film supplementation over a period of several months; only prolonged compliance can achieve clinically detectable benefits that extend beyond the immediate palliative support provided by artificial tear supplements that is reflected in early symptomatic improvement. Interestingly, previous studies investigating similar lipomimetic formulations with shorter followup periods have demonstrated improvements in tear film stability at earlier time points between two weeks to three months, although it is noted that the minimum period of time between drop instillation and evaluation of tear film stability at each clinical visit were not specified in these studies, and also fluorescein breakup time rather than non-invasive tear film stability was assessed in some cases.[7,8,35] The effects demonstrated in the present study, instead reflect a more sustained response, given that the non-invasive measurements were performed at least 90 minutes after drop instillation. Such disparities reinforce the need for longer clinical trials with robust design and harmonised outcome measures. [11,36] The findings of the present study, however, align with the current understanding of the natural history of DED, wherein corneal and conjunctival staining are recognised to be hallmarks of later, more severe stages in the progression of DED. [37–39] A delayed onset of such changes might then, consequently, be expected to require prolonged treatment to resolve. It

is possible, therefore, that the benefits of slow consolidation of the lipid layer over time may be revealed only in long-term efficacy assessments.

DED, according to the TFOS DEWS II diagnostic criteria [11], was resolved in almost one in five participants after six months of drop use. Improvements in signs and symptoms without an accompanying change in lipid layer grade with the non-lipid formulation suggest that observed clinical benefits may not be exclusively ascribed to lipid supplementation. While improvements with the lipid-based drops were most significant for lipid-deficient patients in the current study, the non-lipid formulation appeared to promote comparable positive outcomes for those without lipid insufficiency. In these cases, aqueous supplementation may offer an adequate, and more cost-effective solution; however, the lipid-based formulation may provide broader, sustained relief across the entire disease spectrum (Figure 4). Of note, one in three participants did not respond to even modern artificial tear therapy, but the data suggests this can be determined by one month, allowing alternative management strategies to be trialled in clinical settings.

The severity range of dry eye disease was limited in the current study as a result of its robust design and long-term nature, which could not accommodate the multifaceted approach to management that is often needed in severe DED. [1] The mild-moderate DED status of the cohort may thus have restricted the opportunity to detect significant change in some markers. Osmolar improvements, for example, require abnormal initial levels; [40] however, in this study only limited numbers demonstrated hyperosmolarity at baseline. Future trials would benefit from inclusion of a broader range of disease severity and subtypes to more fully illustrate the potential benefits and understand the mechanisms by which DED can be managed with artificial tear supplements.

CONCLUSION

This study, comparing lipid and non-lipid eye drop formulations, features an extensive, clinically informative follow-up period and a robust study design backed by global consensus diagnostic criteria, to help address key gaps in the scientific literature.

Lipid and non-lipid based artificial tear solutions offer rapid symptomatic relief within a month of regular, daily use. More profound, structural improvements in tear film and ocular surface integrity were observed, but only after several months of use. Preparations with and without a lipid component demonstrated long-term efficacy and a good tolerability profile across a range of dry eye subtypes, although the preferential use of lipid-based preparations for the management of patients exhibiting evaporative DED is recommended.

Restoring and maintaining tear homeostasis over time appears to have a therapeutic, rather than solely palliative effect, endorsing regular drop use as a preventive strategy against the progression of dry eye disease. The study outcomes present compelling reasons to prioritise future longer-term research investigations of tear film supplementation efficacy and lend support to benefits of extended use of regularly applied ocular lubricants.

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CONFLICTS OF INTEREST

The authors have no commercial or proprietary interest in any concept or product described in this article.

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505 **TABLES**

506

507 **Table 1:** Order of clinical assessments conducted at days 0, 30, 60, 90, 120, 150 and 180.

Assessments	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
OSDI dry eye questionnaire	x	x	x	x	x	x	x
SANDE dry eye questionnaire	x	x	x	x	x	x	x
Best corrected visual acuity	x	x	x	x	x	x	x
Blinking assessment	x	x	x	x	x	x	x
Conjunctival hyperaemia	x	x	x	x	x	x	x
Tear meniscus height	x	x	x	x	x	x	x
Non-invasive tear film breakup time	x	x	x	x	x	x	x
Tear film lipid layer grade	x	x	x	x	x	x	x
Tear osmolarity	x	x	x	x	x	x	x
Slit lamp biomicroscopy examination	x						x
Ocular surface staining	x	x	x	x	x	x	x
Meibomian gland expressibility	x						x
Infrared meibography	x						x

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510 **Table 2:** Demographic characteristics of participants randomised to lipid and non-lipid
511 containing eye drops. Data are presented as mean±SD, or number of subjects (% of
512 subjects).

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Characteristic	Lipid drop (n=50)	Non-lipid drop (n=49)	p
Demographics			
Age (years)	45±16	43±17	0.45
Female sex	34 (68%)	32 (65%)	0.83
Ethnicity			
European ethnicity	26 (52%)	24 (49%)	0.90
East Asian ethnicity	12 (24%)	10 (20%)	
South Asian ethnicity	8 (16%)	10 (20%)	
Other ethnicity	4 (8%)	5 (10%)	

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517 **Table 3:** Mixed-effects model analysis of variance of measurements for treatment, time and
518 interaction (treatment-by-time) effects. Ordinal data were analysed using multiple ordinal
519 regression. Data are presented as p-values. Asterisks denote statistically significant effects
520 ($p<0.05$).

521

Measurement	p-value		
	Treatment	**Time**	**Interaction**
Visual acuity			
Best corrected visual acuity	0.92	0.45	0.45
Dry eye symptomology			
OSDI score	0.22	<0.001*	0.33
DEQ-5 score	0.52	<0.001*	0.79
SANDE score	0.96	<0.001*	0.34
Tear film quality			
Tear meniscus height	0.57	0.73	0.38
Tear film lipid layer grade	0.01*	0.49	0.002*
Non-invasive tear film breakup time	0.64	<0.001*	0.96
Tear osmolarity	0.23	0.47	0.39
Inter-ocular difference in osmolarity	0.50	0.67	0.74
Ocular surface characteristics			
Bulbar conjunctival hyperaemia	0.68	0.14	0.66
Limbal conjunctival hyperaemia	0.83	0.20	0.85
Sodium fluorescein staining score	0.34	<0.001*	0.42
Lissamine green staining score	0.53	0.009*	0.79
Superior lid wiper epitheliopathy grade	0.45	<0.001*	0.94
Inferior lid wiper epitheliopathy grade	0.27	0.07	0.80
Lid margin thickening grade	0.38	0.95	0.41
Lid margin rounding grade	0.53	0.61	0.69
Lid margin notching grade	0.41	0.31	0.59
Lid margin foaming grade	0.88	0.09	0.07
Lid margin telangiectasia grade	0.78	0.34	0.92
Meibomian gland capping grade	0.44	0.83	0.69
Staphylococcal lash crusting grade	0.60	0.43	0.42
Seborrhoeic lash crusting grade	0.65	0.11	0.96
Demodex lash cylindrical dandruff grade	0.97	0.18	0.89
Superior lid meibography grade	0.66	0.14	0.86
Inferior lid meibography grade	0.24	0.07	0.98
Meibum expressibility grade	0.41	0.37	0.66
Expressed meibum quality grade	0.21	0.61	0.39
Blinking assessment			
Blink rate	0.96	0.39	0.12
Proportion of blinks incomplete	0.82	0.13	0.77

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