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The Effect of Optive and Optive Advanced Artificial Tears on the Healthy Tear Film

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ABSTRACT

Purpose: To evaluate the impact of Optive (Allergan, Irvine, CA) and Optive Advanced (Allergan, Irvine, CA) on tear film stability and quality during a one-hour observation period when compared to saline (Pfizer, Perth, WA).

Methods: This was a double-masked, cross-over study. Twenty participants attended three visits, randomly receiving either Optive, Optive Advanced or saline. Oculus Keratograph 5M (Oculus, Arlington, WA, USA), non-invasive keratograph break-up time (NIKBUT), Lipiview (TearScience Inc, Morrisville, NC, USA), lipid layer thickness (LLT) and comfort were measured prior to and 5, 15 and 60 min after drop instillation.

Results: Optive Advanced demonstrated a significant increase in LLT between baseline (57.5 ± 12.3 nm) and both 5 min (67.5 ± 18.8 nm, $p = 0.04$) and 15 min (68.9 ± 17.3 nm, $p = 0.04$) but not 60 min (61.6 ± 14.3 nm, $p = 0.47$). Optive and saline were not different between timepoints for LLT ($p > 0.05$). There was no difference between timepoints for any of the drops for NIKBUT ($p = 0.75$). Comfort was significantly better at 5 min compared to baseline for Optive (8.3 ± 1.2 and 7.3 ± 1.4, respectively, $p = 0.03$) but not different for Optive Advance or saline ($p > 0.05$).

Conclusions: Optive Advanced increased LLT for 15 min following instillation, returning to baseline within one hour. This did not however, translate into an improvement in tear film stability over this time period. Only Optive demonstrated an improvement in comfort.

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Artificial tears; lipid layer thickness; tear film break-up time; dry eye

Introduction

The tear film is vital in maintaining the integrity of the ocular surface.[1–3] It offers immunological protection against infection, hydrates the corneal epithelium, oxygenates and nourishes the cornea and maintains a smooth optical surface essential for good visual acuity.[2,4–7] In the case of dry eye disease, tear film instability can result from an aqueous deficiency and/or increased evaporation of aqueous tears.[7] This in turn leads to hyperosmolarity of the ocular surface, which can result in the apoptosis of epithelial surface cells and trigger inflammatory responses that cause the loss of mucin-producing goblet cells.[8–10] This further exacerbates the instability of the tear film, continuing the dry eye disease cycle, intensifying the development and persistence of symptoms.[9,10]

Tear film supplements are the conventional and mainstream treatment method for mild to moderate dry eye disease.[3,11,12] However, tear film supplements are believed to only provide minimal or transient relief of symptoms as they do not treat the underlying cause of the condition.[11,13] Recently, commercially available tear film supplements have been marketed as being designed to target specific dry eye conditions such as aqueous deficient dry eye or evaporative dry eye as a result of meibomian gland dysfunction (MGD).[10,13,14] Purposefully, tailoring treatment for the specific type of dry eye disease is expected to be more effective to supplement the underlying lipid or aqueous deficiency.[10,15,16] Optive Eye Drops (Allergan, Irvine, CA) are an aqueous-based tear film supplement consisting of carboxymethylcellulose sodium (0.5%) and glycerine (0.9%), designed to lubricate the ocular surface and promote the growth of epithelial cells and to provide osmoprotection.[14] Osmoprotectants aim to prevent a hyperosmolar tear film from damaging the ocular surface.[17] Hence, in theory, osmoprotection is one means by which the vicious cycle of dry eye disease can be broken.[9] Optive Advanced Lubricant Eye Drops (Allergan, Irvine, CA) are a lipid-based tear film supplement consisting of the baseline components of Optive with the addition of polysorbate-80 (0.5%), designed to deliver castor oil to the tear film.[10] Castor oil was first used as a vehicle for cyclosporin A (Restasis, Allergan, Irvine, CA) and has been shown to independently reduce tear evaporation through supplementation of the lipid layer.[18] Both Optive and Optive Advanced include the preservative Purite (0.01% stabilized oxychloro complex). It is not known how these two eye drops specifically affect the lipid layer and subsequent tear film stability, or how long their effect lasts. The purpose of this study was to investigate the effect of these tear film supplements on tear film keratograph break-up time and tear film lipid layer thickness (LLT) when compared to saline over a one-hour period.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/icey.

Materials and methods

Participants

The research described in this study followed the tenets of the Declaration of Helsinki 1966, as revised in 2015. This study was approved by the Institutional Human Research Ethics Committee of the University of New South Wales (approval number HC15769). Informed consent was obtained from 20 participants (14 females, 6 males) with a mean age of 20.7 ± 1.7 years (range: 18–24 years). Sample size calculation was based on a statistical significant difference at 95% confidence and with 80% power, of 3 ± 3 s in NIKBUT, based on a previous study using the Oculus Keratograph 5M.[19] Participants were recruited via approved email notices and advertisements placed on noticeboards in the School of Optometry and Vision Science at the University of New South Wales. Participants were required to meet the following inclusion criteria: (1) be aged between 18 and 45 years, (2) be in good ocular and general health with no indications of active ocular surface disease, (3) be a non-contact lens wearer or not have worn contact lenses wear for at least 24 hours prior to each visit, (4) not use eye drops 36 h prior to the study[13], (5) not have had ocular surgery up to 12 weeks prior to the study, (6) not be pregnant or lactating and (7) have no known allergies to tear film supplements.[13]

Study design

This was a double-masked, crossover study where participants attended three visits, at least 24 h apart and at approximately the same time of day. At each visit, ocular comfort, Oculus Keratograph 5M (Oculus, Arlington, WA, USA) non-invasive keratograph break-up time (NIKBUT) and LipiView (TearScience Inc, Morrisville, NC, USA) tear film LLT were measured prior to drop instillation and at 5 min, 15 min and 60 min after drop instillation. Participants were randomized using randomization.com to receive 60 µL of either Optive (Allergan, Irvine, CA), Optive Advanced (Allergan, Irvine, CA) or unit dose sterile saline (Pfizer, Perth, WA) at each visit. The drop was instilled into the inferior palpebral fold using a pipette and the volume (60 µL) was standardized to simulate the size of an eye drop expelled from a bottle.[20] Both the participants and the investigator taking the measurements were masked to the eye drop, with a second investigator being responsible for eye drop instillation. The order of the Oculus and the LipiView were randomized using randomization.com, as was the eye order of eye drop instillation. Measurements were taken from both eyes.

Ambient room temperature and humidity are considered to have a considerable effect on tear film characteristics,[21,22] hence this study was conducted in an examination room with a constant temperature of 22°C and humidity within the range of 35–50%. Participants were also discouraged from rubbing their eyes during the study to minimize meibomian gland expression.[13,23,24]

Clinical techniques

Comfort

The 12-item self-administered Ocular Surface Disease Index Questionnaire (OSDI, Allergan Inc, Irvine, CA) was used to grade dry eye symptoms. A score of 13 or more was used as the cutoff for dry eye classification[25] and considered an exclusion factor.

Participant assessment of ocular comfort was recorded using a scale of 1–10, where 1 was very poor, 5 was neutral and 10 was excellent.

Visual acuity

Visual acuity was measured at baseline for each visit for safety purposes, using computerized letter charts.[26]

Slit-lamp biomicroscopy

At the start of each visit, the Cornea and Contact Lens Research Unit (CCLRU) scale[27] was used to evaluate bulbar and limbal redness with slit-lamp biomicroscopy (Zeiss SL-120, Carl Zeiss Meditech, Jena, Germany) and to identify pre-existing corneal staining using white light. If any staining of grade 2 and above in extent was detected, the visit was postponed for another day.

Non-invasive keratography break up time

NIKBUT was measured with the Oculus Keratograph 5M (Oculus, Arlington, WA, USA). Both the first break (NIKBUT-1) and the average break (NIKBUT-average) were recorded. Values of 24.73 s were excluded as this was the upper cut-off of the instrument and hence considered unusable. This was the case in 6% of instances.

Lipid layer thickness

Tear film LLT was measured with the LipiView Ocular Surface Interferometer (TearScience Inc, Morrisville, NC, USA). The participant's eye was positioned in front of the illumination source and a 20 s video of the tear film interference was recorded. The thickness of the tear film lipid layer was displayed in interferometric color units (ICU) where 1 ICU is approximately 1 nm of LLT.[28] Values of 100 ICU were excluded as this is the upper cut-off for the instrument and hence considered unusable. This was the case in 13% of instances.

Data analysis

Data were log transformed. A critical p-value of <0.05 was used to denote statistical significance and results are reported as mean ± standard deviation (SD). The data analysis was performed using SAS software, Version 9.4 (2012, SAS Institute Inc., Cary, NC, USA). A linear mixed model with within-subjects fixed effects of time and drop was run on each variable. Estimated marginal means were obtained, and pairwise tests of drop differences at

each time point and of time differences within each drop type were performed, and adjusted for multiple comparisons using Holm's procedure.[29] A series of paired sample tests were run on the right and left eye values to assess whether systematic differences between right and left eye measures existed. Analyses were performed on the averaged right and left eye values. If one of the eyes had a value that was removed due to an invalid value, then the "average" was the value for the other (valid) eye.

Results

Baseline measurements at each visit are shown in Table 1. NIKBUT-average, NIKBUT-1 and LipiView maximum showed the greatest variability between baseline visits, although these were not statistically different.

Lipid layer thickness

Lipiview average

There was no difference in LipiView average between eyes at any visit or with any drop. Therefore, analyses were performed on the averaged right and left eye values.

Test of fixed effects demonstrated a significant effect between drops (p = 0.01), with Optive being higher than Optive Advanced and the saline groups (Figure 1). Unadjusted p-values indicated a significant difference between baseline and the 5-min timepoint (p = 0.04) and baseline and the 15-min timepoint (p = 0.04) for Optive Advanced. When adjusting for multiple comparisons, the p-value was no longer significant. There was no significant change over time (p = 0.051) and no significant drop and time interaction (p = 0.83).

Lipiview minimum

Eyes were different at two study visits for the saline group but this was not a systematic error. Therefore, analyses were performed on the averaged right and left eye values.

Test of fixed effects demonstrated that there was no significant effect between drops (p = 0.09), no difference in change over time (p = 0.09) and no drop by time interaction (p = 0.60) which indicates that the change over time was not different between drops.

Lipiview maximum

There was no difference between eyes at any visit or with any drop. Therefore, analyses were performed on the averaged right and left eye values.

Test of fixed effects demonstrated that there was no effect between drops (p = 0.15), no difference in change over time (p = 0.45) and there was no significant drop and time interaction (p = 0.98). Therefore, there was no evidence of different patterns of change over time among the groups.

NIKBUT

Figures 2 and 3, respectively, illustrate NIKBUT-1 and NIKBUT-average for each tear film supplement over the course of 60 min.

NIKBUT-1

Eyes were different at two study visits for the Optive Advance group but this was not a systematic error. Analyses were performed on the averaged right and left eye values.

Test of fixed effects demonstrated that there was no effect between drops (p = 0.60), no difference in change over time (p = 0.85) and there was no significant drop and time interaction (p = 0.27). Therefore, there was no evidence of different patterns of change over time among the groups.

NIKBUT-average

Eyes were different at one study visit for the Optive Advanced group but this was not a systematic error. Analyses were performed on the averaged right and left eye values.

Test of fixed effects demonstrated that there was no effect between drops (p = 0.75), no difference in change over time (p = 0.56) and there was no significant drop and time interaction (p = 0.70). Therefore, there was no evidence of different patterns of change over time among the groups.

Comfort

Figure 4 illustrates the mean ± SD comfort for each drop over the one hour observation period. The model showed no significant drop and time interaction (p = 0.92). The main effect

Table 1. Baseline characteristics calculated based on the baseline measurements taken at each visit.

Baseline characteristic	Visit 1	Visit 2	Visit 3
Bulbar redness – right eye	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.3
Bulbar redness – left eye	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
Limbal redness – right eye	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3
Limbal redness – left eye	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
NIKBUT-First break – right eye (s)	11.3 ± 8.2	8.8 ± 6.2	10.8 ± 7.7
NIKBUT-First break – left eye (s)	12.4 ± 6.1	9.2 ± 4.5	9.6 ± 6.6
NIKBUT-Average break – right eye (s)	14.0 ± 7.1	11.7 ± 5.7	13.1 ± 6.9
NIKBUT-Average break – left eye (s)	14.9 ± 5.2	13.1 ± 5.3	12.3 ± 5.9
Lipiview-Max – right eye (nm)	69.1 ± 17.5	75.4 ± 21.7	58.2 ± 20.8
Lipiview-Max – left eye (nm)	67.1 ± 15.0	67.5 ± 18.2	64.6 ± 18.3
Lipiview-Min – right eye (nm)	48.2 ± 14.8	53.0 ± 20.5	51.3 ± 18.7
Lipiview-Min – left eye (nm)	52.7 ± 15.4	57.9 ± 20.0	51.0 ± 21.9
Lipiview-Ave – right eye (nm)	55.4 ± 13.6	61.9 ± 18.2	57.2 ± 22.7
Lipiview-Ave – left eye (nm)	59.2 ± 15.5	65.1 ± 21.3	54.9 ± 16.8
Comfort score (1–10 range)	7.2 ± 1.6	7.3 ± 1.4	7.3 ± 1.4
Ocular Surface Disease Index	13.5 ± 6.1		

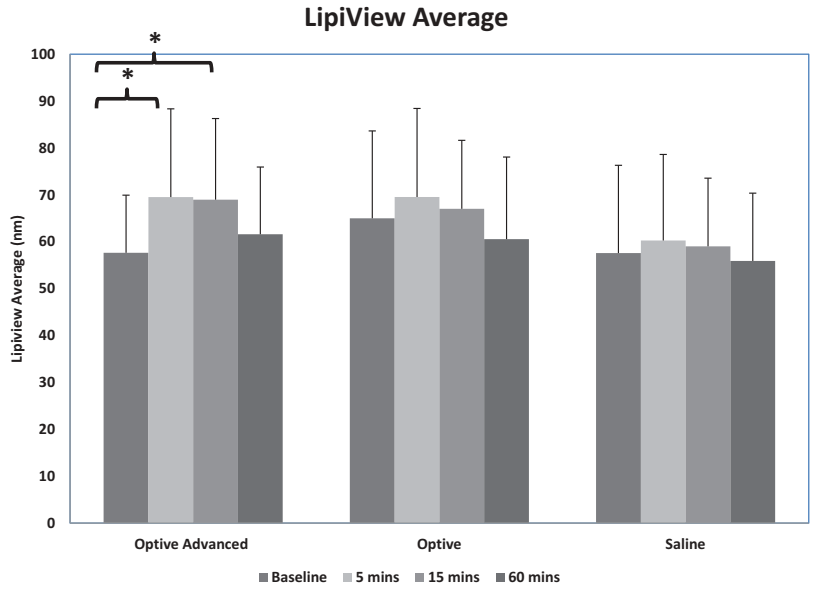

Figure 1. LipiView average measurements (mean ± standard deviation) at baseline and at 5, 15 and 60 min after instillation of Optive Advanced, Optive and saline. Right and left eyes were averaged. An asterisk (*) denotes statistical significance.

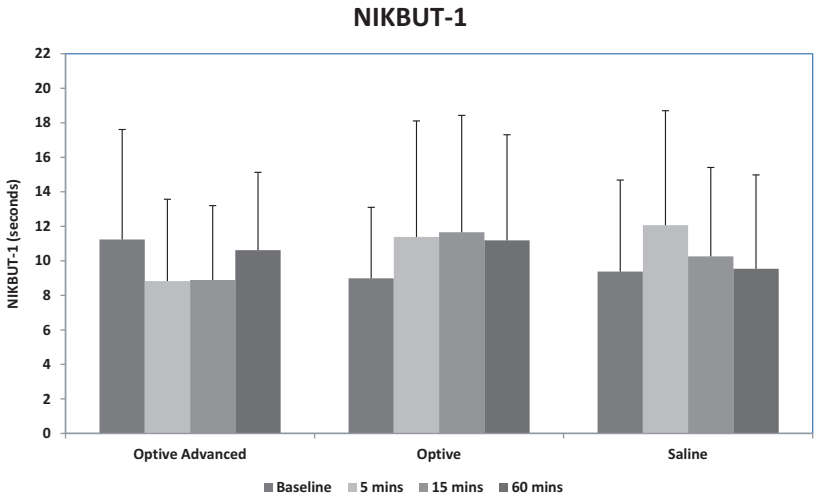

Figure 2. The first non-invasive keratograph break-up time measurements (NIKBUT-1, mean ± standard deviation) at baseline and at 5, 15 and 60 min after instillation of Optive Advanced, Optive and saline. Right and left eyes were averaged. There were no significant differences between timepoints or between drops.

of time was not significant ($p = 0.62$). There was a main effect of drop ($p = 0.04$), where Optive had overall higher comfort scores. Unadjusted p values indicate a significant difference between baseline and 5 min for Optive only ($p = 0.03$).

Discussion

This study demonstrated an increased LLT for 15 min following instillation with Optive Advance, with LLT returning to baseline levels within one hour. This did not translate to an improvement in tear film stability as indicated by NIKBUT and only Optive demonstrated an improvement in comfort.[30]

The castor oil in Optive Advanced is intended to restore the osmolarity of the tear film and reduce tear evaporation from the ocular surface.[16,31–33] It has previously been reported that castor oil causes enhanced meibomian gland secretions, increasing the LLT.[16,31] Our findings support this observation, with Optive Advanced being the only drop to demonstrate an increase in LLT. While our study demonstrated a return to baseline within one hour, Maissa et al. found that a castor oil emulsion achieved a residence time of at least 4 h when observed subjectively with the Keeler Tearscope-Plus in normals and dry eye patients and when tears were analyzed with high performance liquid chromatography.[16] The decline in LLT with Optive Advanced one hour after instillation may be due to the lower volume of castor oil relative to the other components within the drop, reducing its longevity in the tear film. Our results suggest that more regular dosing is required in order to achieve a longer residence of the Optive Advanced in the tear film. Optive and saline on the other hand had no effect on LLT during the observation period, which was to be expected. Similarly, when Wojtowicz et al. used an evaporometer to compare the tear

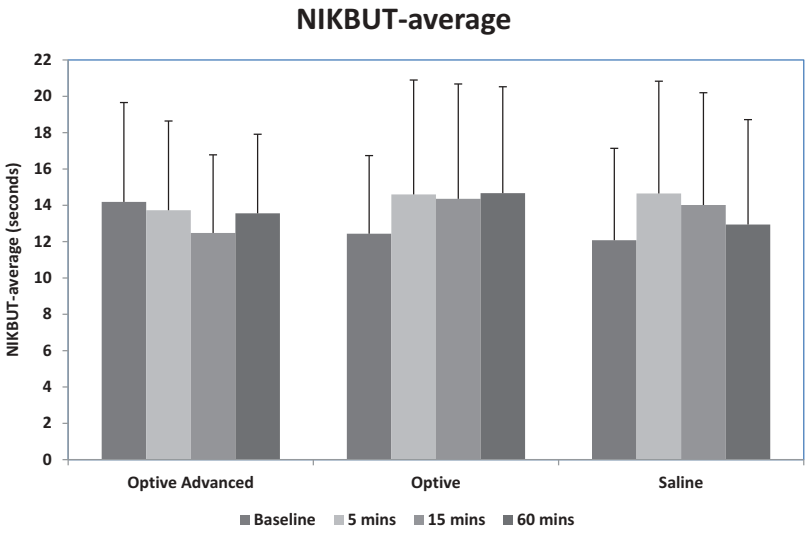

Figure 3. The average non-invasive keratograph break-up time measurements (NIKBUT-average, mean ± standard deviation) at baseline and at 5, 15 and 60 min after instillation of Optive Advanced, Optive and saline. Right and left eyes were averaged. There were no significant differences between timepoints or between drops.

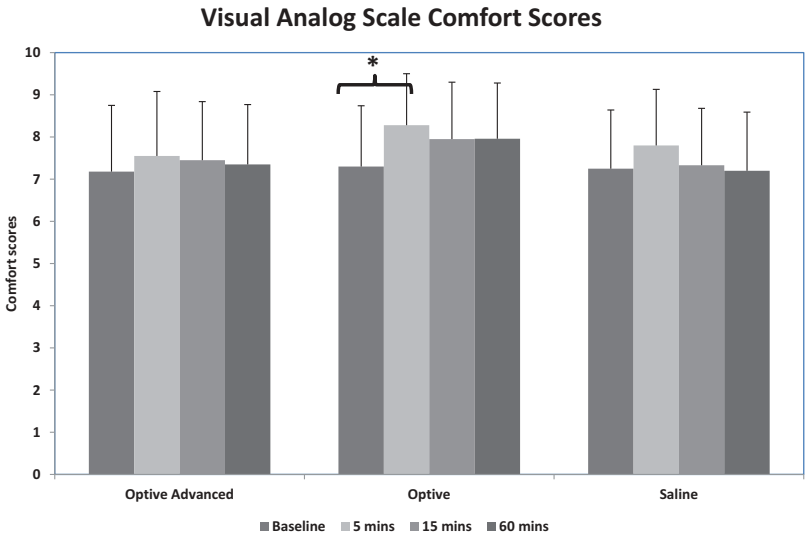

Figure 4. Comfort (mean ± standard deviation) at baseline and at 5, 15 and 60 min after instillation of Optive Advanced, Optive and saline. Right and left eyes were averaged. An asterisk (*) denotes statistical significance.

evaporation rates of Optive and Systane (Alcon Laboratories, Fort Worth, TX) 30 min post-instillation,[14] no difference was found from baseline for either drop.[14]

Despite the improved LLT with Optive Advanced, this did not translate to an improvement in tear film stability as measured with NIKBUT for any of the drops at any time-point, consistent with Wojtowicz.[14] This study was powered to detect a significant difference in NIKBUT. A post-hoc power calculation confirms that the study was sufficiently powered to address this. LLT as measured with the LipiView has been previously reported to show no association with tear film break-up time.[23,34] The literature has been equivocal with regards to the effect of lubricants on tear film break-up time, perhaps due to the differing methods used to measure tear film stability. Evangelista et al. measured fluorescein tear break-up time over a one-hour period following the instillation of Optive,[1] and reported a significant increase in tear break-up time one hour after instillation, but not at the 15-min mark.[1] Calvão-Santos found a significant improvement in the tear break-up time following 30 days of Optive use in computer users and contact lens users with dry eye.[35] In alignment with our findings, Lanzini et al. also did not find a change in tear film parameters.[36] In their contralateral study on participants with dry eye disease, one eye was allocated Optive and the other eye was allocated Hylogel (Visufarma spa), each four times daily for 90 days.[36] During the follow-up period, there was no significant difference in tear break-up time or in the Schirmer I test score, however both groups showed an improvement in lissamine green staining of the ocular surface,[36] a finding supported by Guillon et al.[37] Lanzini et al. also reported an increase in the regularity of corneal and conjunctival cell shape and size with both drops as shown with *in vivo* confocal microscopy.[36] The Optive

group demonstrated a reduction in conjunctival epithelial cell matrix metalloproteinase-9 (MMP-9) and interleukin-6 levels.[36] As MMPs play a role in the inflammatory pathway-[38] and are expressed in hyperosmolar conditions,[39] this down-modulation, as well as the decrease in IL-6 is consistent with an anti-inflammatory effect, as shown for unpreserved lubricants.[40] This indicates that while Optive and Optive Advanced do not result in a measurable improvement in tear film stability, their effect on dry eye may be via osmoprotection. L-carnitine, found in both Optive and Optive Advanced,[1,10] plays a vital role in protecting the ocular surface from hyperosmolarity by exerting marked osmolytic activity.[1,10] As tear hyperosmolarity exacerbates tear film instability, further encouraging the dry eye disease cycle,[9] the instillation of L-carnitine may help restore or maintain tear film stability.[1]

A thin lipid layer in the tear film has been known to correlate with a reduced level of ocular comfort and an increase in tear film instability.[13,41,42] Hence an increase in LLT is believed to correspond with improved ocular comfort.[13,16] However, this study did not include symptomatic participants, thereby making it more difficult to discern an improvement in comfort. In one multicenter study, participants with dry eye disease were allocated Optive for a 2–4 week period and an improvement was noted in comfort and in tear film break-up time at the conclusion of the study.[43]

A limitation of this study is the inclusion of only healthy, asymptomatic, non-dry eye participants. Despite the inclusion criteria, some participants had LLT that could be considered to be thin (range of LipiView Minimum being 22–100 nm at baseline), suggesting that some participants may have had underlying MGD. Further investigation is required to determine the effect of Optive Advanced and Optive on participants diagnosed with both evaporative dry eye disease and aqueous deficiency. In addition, it would be of interest to determine the effect of more regular dosing over longer periods, as well as the effect of a longer observation period to determine the longer-term effect of these lubricants.

In conclusion, Optive Advanced increased LLT for 15 min following instillation, with LLT returning to baseline levels within one hour, indicating the need for more frequent dosing. This did not translate to an improvement in tear film stability. Only Optive demonstrated an improvement in comfort.

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Declaration of Interest

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