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Evaluation of Systane Complete for the Treatment of Contact Lens Discomfort

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ABSTRACT

Purpose: To understand if a new artificial tear, which is indicated for the treatment of both evaporative and aqueous deficient dry eye, is able to safely alleviate contact lens discomfort (CLD) in symptomatic soft contact lens (CL) wearers.

Methods: This registered, investigator-masked, two-week, randomized clinical trial recruited adult subjects with symptomatic Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8 scores ≥ 12) scores. Subjects were randomized to use artificial tears (Systane Complete) before and after CL use or no treatment. Clinical signs (visual acuity, tear breakup time, corneal staining, Schirmer's test I, and meibum quality and expression) and symptoms (CLDEQ-8, Standardized Patient Evaluation of Eye Dryness (SPEED), self-reported) were evaluated at baseline and two weeks.

Results: This study recruited 22 subjects who were randomized to artificial tears and 24 subjects who were randomized to no treatment. Subjects in the artificial tears group had significantly better CLDEQ-8 scores (12.86 ± 6.40 vs. 17.92 ± 5.30 ; $p = 0.006$) but not SPEED scores (7.55 ± 4.31 vs. 9.29 ± 4.14 ; $p = 0.17$) at two weeks compared to the no treatment group. No significant between group differences were noted for any clinical signs at two weeks (all $p > 0.29$). No subject in either group reported any adverse events during the study.

Conclusions: Systane Complete was found to safely and significantly improve CL comfort in symptomatic CL wearers. Additional work is needed to better understand the mechanism(s) leading to improved comfort since tested clinical signs were unchanged.

1. Introduction

Despite numerous improvements in soft contact lens materials and solutions, the advent of daily disposable contact lenses, and the availability of rewetting drops that are specifically designed to improve contact lens comfort, research has shown that up to 64% of all contact lens wearers permanently discontinue wearing contact lenses because of contact lens-related discomfort [1–4]. Contact Lens Discomfort has been defined as a specific “condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear” [5]. Contact Lens Discomfort is considered to be a multifactorial affliction that is instigated by both contact lens (e.g., material design, fit) and

environmental factors (e.g., patient factors, ocular environment) [5]. While patient characteristics such as age and sex cannot be changed, new comfort drop (artificial tear) formulations have the potential to treat tear film deficiencies that may be promoting Contact Lens Discomfort [6,7].

A frequent first-line treatment for Contact Lens Discomfort is contact lens rewetting drops, which are regulated under the U.S. Food & Drug Administration's (FDA) *Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products* [8]. The U.S. FDA has defined a rewetting drop as “an in-eye solution for use with CLs” that contains “one or more active ingredients (e.g., ophthalmic demulcents) in sufficient concentration to alleviate symptoms of discomfort from contact lens wear by physical means” [8]. While rewetting drops are similar to artificial tears, artificial tears are distinctly defined under the U.S. FDA's *Ophthalmic Drug Products for Over-the-Counter Human Use* monograph as

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topical drops, which contain specific types of demulcents or emollients for the treatment of dry eye or ocular discomfort [9]. This separate distinction between these two types of drops may have originated because early artificial tear formulations contained preservatives such as benzalkonium chloride or thimerosal [10,11], which have historically been thought to be incompatible with contact lenses because prolonged exposure to these preservatives may promote corneal damage [11,12]. Nevertheless, manufacturers have since developed new gentler preservatives for use in topical drops that are more compatible with the eye (e.g., polyquaternium-1) and are now commonly used to help protect multiuse artificial tears from microbial contamination [6,7,13].

The safety of modern artificial tears with contact lenses has been previously studied. McDonald et al. has specifically shown that using a common artificial tear, Systane Ultra (Alcon, Fort Worth, TX), which is preserved with polyquaternium-1, before and after contact lens use is an effective means for treating symptomatic daily disposable contact lens wearers as compared to a no treatment control group [7]. Likewise, Kading has shown that direct application of Systane Ultra to contact lenses is safe [6]. Recently, a new formulation of artificial tears, Systane Complete (Alcon, Fort Worth, TX), which is also preserved with polyquaternium-1, was released to the market. Systane Complete is a unique artificial tear formulation that combines elements from both Systane Ultra (indicated for aqueous deficient dry eye) and Systane Balance (indicated for evaporative dry eye) to create a new artificial tear with an indication for aqueous deficient, evaporative, and mixed aqueous deficient and evaporative dry eye. Therefore, the purpose of this study was to determine in a randomized, investigator-masked, clinical trial if Systane Complete is able to effectively improve the discomfort symptoms of daily disposable contact lens wearers. This study secondarily attempted to determine if Systane Complete was safe to use before and after contact lens use and to determine how Systane Complete impacts the ocular signs of contact lens wearers.

2. Methods

2.1. Subjects

This two-week, two-visit study was conducted at the University of Alabama at Birmingham (Birmingham, AL, USA), Southern College of Optometry (Memphis, TN, USA), and Lindenhurst Eye Physicians & Surgeons, P.C. (Babylon, NY). A two-week long study was considered appropriate based upon past studies and based upon artificial tears directly supplementing the ocular surface upon drop application [6,7,14]. Subjects were recruited from each site via clinic records, postcards, email, social network posting, or fliers. Adult (≥ 18 years) daily disposable contact lens wearers who had 20/30 Snellen visual acuity or better and who had symptomatic Contact Lens Dry Eye Questionnaire (CLDEQ)-8 scores (CLDEQ-8 scores ≥ 12) were recruited [15]. Other contact lens modalities and wear schedules (e.g., two-week and monthly replacement contact lenses, gas permeable contact lenses) and non-compliant daily disposable contact lens users (must replace contact lenses daily) were excluded to avoid any potential confounders associated with contact lens care systems. Subjects were asked to wear their habitual daily disposable contact lenses as prescribed each day of the study. Subjects were excluded if they had a systemic health conditions that is known to alter tear film physiology (e.g., primary and secondary Sjögren's syndrome), a history of ocular surgery within the past 12 months, a history of severe ocular trauma, an active ocular infection or inflammation, were currently using isotretinoin-derivatives or ocular medications, or if they were pregnant or breast feeding [16]. Subjects with a condition or in a situation, which in the examiner's opinion, may have put the subject at significant risk, may confound the study results, or may have significantly interfered with their participation in the study were excluded (e.g., in ability to follow study directions). Subjects with non-Sjögren's dry eye disease and subjects who had mild corneal scarring (no corneal elevations changes) were allowed

to participate. Subjects who were currently using artificial tears or rewetting drops were allowed to participate, though they were required to not use the drops for at least 24 h before the baseline study visit; these subjects were also asked to not use their habitual drops for the duration of the study. This study received Institutional Review Board approval from the University of Alabama at Birmingham (IRB300002321) and Southern College of Optometry (IRB0004673). This study conformed to the Declaration of Helsinki, and it was registered with Clinicaltrials.gov (NCT03682809).

2.2. Sample size

Contact Lens Dry Eye Questionnaire (CLDEQ)-4 scores (Rasch validated version; max score of 18) were used to calculate the sample size [17]. The CLDEQ-4 (subset of CLDEQ-8 questions), which is fully described in Pucker et al., was selected because the CLDEQ-4 has been found to be a unidimensional measure of ocular discomfort in contact lens wearers [17]. Data from Pucker et al. suggests that the average contact lens wearer has a mean CLDEQ-4 score of 7.6 ± 3.8 [17]. A 4-point difference in CLDEQ-4 scores was considered to be a clinically meaningful improvement in contact lens comfort. Sample size calculations determined that 19 subjects per group were needed to determine if there were no significant differences in contact lens comfort between the Systane Complete (artificial tear group) and no treatment groups at the two-week visit (power = 90%; alpha = 0.05). The sample size was inflated by 20% to account for any potential attrition; this yielded a final sample size of 46 subjects.

2.3. Subject groups and randomization

This was a prospective, investigator-masked, randomized, clinical trial. Subjects who meet all study criteria were enrolled and randomized into the study. Subject randomization was organized by the data coordinator (GM) through Research Electronic Data Capture (REDCap) [18]. The randomization schedule utilized blocking (given the small sample size) and stratification by site to maximize the likelihood that study subjects would be equally distributed between the treatment groups and by site. Subject group assignments were concealed from the masked examiners. Specifically, after a subject was enrolled in the study and after the masked examiner had left the examination area, the unmasked study coordinator accessed REDCap to retrieve the qualifying subject's study group assignment (artificial tears vs. no treatment). The unmasked study coordinator then educated the subject about their group assignment. Subjects who were randomized to the treatment (artificial tears) group received a de-identified bottle of artificial tears (Systane Complete with markings and labels removed). If a subject was randomized to the artificial tears group, the unmasked study coordinator educated the subject on how to use the artificial tears (2 times per day in each eye; once 10 min before and once directly after contact lens wear). All subjects were instructed to not divulge any information related to their assigned group to the masked examiner. All subjects were also specifically instructed to not use other artificial tears or rewetting drops or eye drops during the study. Both groups were dispensed a contact lens comfort log, which asked the subjects to record artificial tear application times (if applicable), wear time, and comfortable wear time at one day, one week, and two weeks for both eyes simultaneously. Subjects also recorded daily end-of-day contact lens comfort on a visual analog scale (0–100 scale with 100 indicating best comfort possible) for both eyes simultaneously, which was created by the examiners.

2.4. Questionnaires and clinical tests

Clinical measurements were obtained from both eyes and testing was performed in the described below order; worse eye by clinical sign was included in the analyses. This methodology was used because the

eye with the worse clinical sign would be the eye expected to drive patient reported symptoms. Testing order was designed to be sequentially administered with the least invasive test first and the most invasive test last. This approach was taken ensure that previous tests had minimal impact on subsequent tests [19]. All questionnaire and clinical data were captured with www.qualtrics.com (Qualtrics, Provo, UT, USA). Subjects were asked to report to the study without their contact lenses on for at least 30 min to minimize the effect of contact lens removal on the study outcomes. However, subjects were asked to complete all questionnaires as if they were currently wearing their contact lenses at the end-of-the-day. While this method may result in some recall bias, it is unlikely because subjects were only being asked to recollect the past day. This approach was also required to facilitate subject scheduling and to avoid introducing bias related to removing contact lenses and collecting tear film measurements.

The baseline visit began by having the subject repeat the IRB approved phone screening questionnaire in order to verify the subject's eligibility. The subject also repeated the CLDEQ-8 questionnaire (CLDEQ-8 scores ≥ 12) to verify that they were symptomatic contact lens wearers as part of this phone screening device. Qualifying subjects were then consented and after appropriate signatures were obtained the subjects were asked to complete an investigator created health history questionnaire, which recorded ocular and systemic health history. The health history questionnaire also contained questions about current artificial tear usage. Subjects were next asked to complete the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire because it is a dry eye symptoms questionnaire that is validated for use in contact lens wearers; it was also selected because it asks about the frequency and severity of the most commonly reported dry eye symptoms (dryness, grittiness, or scratchiness, soreness or irritation, burning or watering, and eye fatigue) [20].

The clinical assessment included Bailey-Lovie high-contrast (logMAR) visual acuity, a slit-lamp biomicroscope evaluation of the eyelids, cornea, and conjunctiva, tear break-up time, corneal staining, Schirmer's I test (without anesthesia), and an evaluation of the meibomian glands. Tear break-up time was performed by wetting a sodium fluorescein strip with sterile saline and applying it to the superior bulbar conjunctiva. After waiting one minute, the subject was asked to position themselves within the slit-lamp biomicroscope and blink three times. The subject was then asked to keep their eyes open and to not blink for as long as possible. The investigator used a stopwatch to determine the number of seconds between the last blink and first tear break-up as viewed with cobalt blue light and a Wratten yellow filter. If a blink did occur, this was recorded as the moment of tear break-up. The subject was then allowed to blink normally for ten seconds before repeating the procedure. Each eye's tear break-up time was measured in triplicate, and the mean of each eye was used in analysis. Corneal staining was then evaluated with the already applied sodium fluorescein and the same viewing conditions used during tear break-up time. The Brien Holden Vision Institute (BHVI) grading scale was used to evaluate corneal staining (0–4 grading scale for extent, type, and depth) in five corneal regions (max 20 units per metric); the individual sums of all five regions for extent, type, or depth were used in analysis [21]. Schirmer's test I without anesthetic was used to evaluate tear volume by placing the Schirmer's strip at the temporal third of each lower eyelid.

The subject was asked to close their eyes for five minutes, and the length of wetting was then measured and recorded in mm. Meibomian gland health (meibum expressibility and quality) was evaluated to help characterize the subject's dry eye status. Meibomian gland expressibility and quality of the central eight meibomian glands of the upper and lower eyelids were evaluated by having the investigator slightly evert the eyelids and apply light pressure for about 15 s about one millimeter distal to the eyelash line. Meibomian gland expressibility (0–3 scale) and quality (0–4 scale) were then graded with Meadows et al.'s grading scale [22]. Subjects were then randomized and educated as described above, provided with a contact lens compliance log, and scheduled for their two-week outcome visit. Treatment compliance was defined as using the artificial tears at least 90% of the time per the contact lens compliance log. When subjects returned for their two-week visit, the CLDEQ-4/8 and SPEED questionnaires were repeated, and the same clinical testing protocol was performed. Completed subjects were asked by the masked examiner without unmasking themselves if their perceived eye comfort was the same, better, or worse compared to the baseline visit. The masked examiner then left the room, and the unmasked study coordinator revealed the treatment to the subject. The subject was then exited from the study.

2.5. Statistical analysis

All data were analyzed with SAS Version 9.4 (SAS; Cary, NC, USA). The intention to treat analysis method was employed. The treatment groups were compared with respect to demographic and baseline characteristics to test for successful randomization. T- and chi-square tests were used when comparing continuous and categorical variables, respectively. When comparing the primary outcome measure (CLDEQ-4 scores) between the treatment groups, generalized linear models were used with the follow-up measurement as the dependent variable and treatment group and baseline measurement used as independent variables. This approach ensured that if there were any differences between the study groups, the between group comparison would be independent of differences at the baseline visit. For comparing changes in outcome measures within treatment groups, Wilcoxon Signed Rank tests were used.

3. Results

This study recruited 46 symptomatic daily disposable contact lens wearers with the demographic characteristics described in Table 1. Twenty-two subjects were allocated to the treatment group while 24 subjects were allocated to the control group; all subjects who were randomized into the study completed the study (Fig. 1). Twenty-two (22.73) percent of the treatment group and 20.83% of the control group had self-reported dry eye while no subjects in the treatment and 22.73% of the control group had self-reported ocular allergies (Table 1). Fifty-nine (59.09) percent of the treatment group were habitually using artificial tears or rewetting drops before the study while 45.83% of the control group were using artificial tears or rewetting drops before the study (Table 1). With the exception of self-reported ocular allergies being more common in the treatment group compared to the no treatment group ($p = 0.02$), there were no significant between-group

Table 1
Subject Demographics by Study Group.

Characteristic	Treatment Group: Systane Complete	Control Group: No Treatment	Group Comparisons (P-Value)
Age (Years)	32.7 \pm 13.1	28.8 \pm 11.2	0.29
Female (%)	9.1	20.8	0.42
Patient Reported Dry Eye Diagnosis (Yes %)	22.73	20.83	1.00
Patient Reported Ocular Allergies Diagnosis (Yes %)	22.73	0	0.02
Artificial Tear or Rewetting Drop Usage (Yes %)	59.09	45.83	0.39

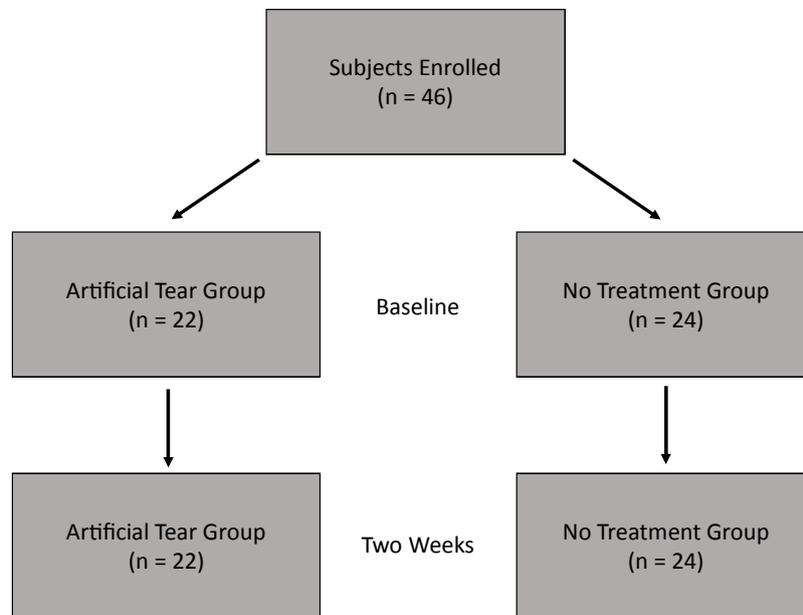


Fig. 1. Study Flow Diagram.

Table 2
Baseline Clinical Characteristics by Study Group (Worse Eye).

Characteristic	Treatment Group: Systane Complete (Mean ± SD)	Control Group: No Treatment (Mean ± SD)	Group Comparisons (P-Value)
Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8)	20.41 ± 5.40	18.92 ± 4.92	0.25
Contact Lens Dry Eye Questionnaire-4 (CLDEQ-4)	10.91 ± 3.28	10.38 ± 2.41	0.42
Standardized Patient Evaluation of Eye Dryness (SPEED)	10.27 ± 3.60	9.67 ± 3.93	0.90
Visual Acuity (logMAR)	0.05 ± 0.17	0.11 ± 0.21	0.39
Mean Sodium Fluorescein Tear Break Up Time (seconds)	7.70 ± 5.20	8.50 ± 5.10	0.57
Corneal Staining (Brien Holden Vision Institute Grading Scale)			
Extent (0-20 scale)	1.73 ± 2.45	1.63 ± 2.50	0.60
Depth (0-20 scale)	1.22 ± 1.54	0.92 ± 1.32	0.42
Type (0-20 scale)	1.18 ± 1.56	0.92 ± 1.32	0.55
Schirmer's Test (mm)	15.68 ± 9.70	20.88 ± 10.65	0.11
Meibum Quality – Upper Eyelid (0-4 scale)	1.23 ± 1.48	1.04 ± 1.12	0.99
Meibum Quality – Lower Eyelid (0-4 scale)	1.05 ± 1.17	1.04 ± 1.04	0.89
Meibum Expressibility – Upper Eyelid (0-3 scale)	1.18 ± 1.14	1.21 ± 1.06	0.89
Meibum Expressibility – Lower Eyelid (0-3 scale)	1.41 ± 1.10	1.21 ± 0.98	0.58

Table 3
Baseline Contact Lens History by Study Group.

Characteristic	Treatment Group: Systane Complete (Mean ± SD)	Control Group: No Treatment (Mean ± SD)	Group Comparisons (P-Value)
Age at first Contact Lens Use (years)	20.63 ± 13.73	17.58 ± 11.17	0.70
Days of Contact Lens Use Per Week	6.09 ± 1.23	5.50 ± 1.59	0.19
Hours of Contact Lens Use Per Day	7.73 ± 0.94	7.71 ± 1.00	0.94
Hours of Comfortable Contact Lens Use Per Day	5.82 ± 1.74	5.58 ± 2.04	0.78
Satisfied or Very Satisfied with Contact Lens Comfort (%)	72.73	58.33	0.54
Satisfied or Very Satisfied with Vision in Contact Lenses (%)	77.27	87.50	0.83

differences with respect to subject demographics or baseline clinical characteristics (All $p > 0.11$; [Tables 1 and 2](#)). There were also no significant between-group differences with regards to contact lens wearing experience, wearing habits, satisfaction with contact lens comfort, or satisfaction with vision in contact lenses (All $p > 0.19$; [Table 3](#)).

This study found that 95% of the subjects in the treatment group were compliant. CLDEQ-8 ($p < 0.006$) and CLDEQ-4 ($p < 0.005$) scores were significantly better in the artificial tear group at two weeks compared to the no treatment group ([Table 4](#)). There was no significant

difference ($p = 0.17$) between the artificial tear and no treatment groups with regards to SPEED scores at two weeks. Subjects in the treatment group were significantly ($p < 0.001$) more likely to report that their perceived eye comfort was “better” at two weeks compared to the control group. There were no significant between-group differences for the clinical signs described in [Table 4](#) (All $p > 0.29$) at two weeks.

The treatment group had significantly (All $p < 0.0001$) better symptoms scores (CLDEQ-8, CLDEQ-4, SPEED) at two weeks compared to baseline while the control group did not have significantly (All $p > 0.26$) different symptoms at two weeks compared to baseline

Table 4
Outcome Clinical Characteristics by Study Group at Two Weeks (Worse Eye).

Characteristic	Treatment Group: Systane Complete (Mean \pm SD)	Control Group: No Treatment (Mean \pm SD)	Group Comparisons (P-Value)
Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8)	12.86 \pm 6.40	17.92 \pm 5.30	0.006
Contact Lens Dry Eye Questionnaire-4 (CLDEQ-4)	7.14 \pm 3.50	10.13 \pm 2.83	0.005
Standardized Patient Evaluation of Eye Dryness (SPEED)	7.55 \pm 4.31	9.29 \pm 4.14	0.17
Visual Acuity (logMAR)	0.10 \pm 0.24	0.04 \pm 0.15	0.52
Mean Sodium Fluorescein Tear Break Up Time (seconds)	8.57 \pm 4.73	8.80 \pm 5.08	0.98
Corneal Staining (Brien Holden Vision Institute Grading Scale)			
Extent (0-4 scale)	1.41 \pm 2.42	1.75 \pm 1.98	0.29
Depth (0-4 scale)	0.91 \pm 1.38	1.04 \pm 1.30	0.48
Type (0-4 scale)	0.86 \pm 1.36	0.92 \pm 1.06	0.46
Schirmer's Test (mm)	15.41 \pm 9.29	18.30 \pm 10.69	0.35
Meibum Quality – Upper Eyelid (0-4 scale)	0.77 \pm 1.19	0.96 \pm 1.23	0.55
Meibum Quality – Lower Eyelid (0-4 scale)	0.59 \pm 0.73	0.87 \pm 0.99	0.34
Meibum Expressibility – Upper Eyelid (0-3 scale)	1.05 \pm 1.00	1.33 \pm 1.13	0.38
Meibum Expressibility – Lower Eyelid (0-3 scale)	1.27 \pm 0.94	1.13 \pm 0.95	0.64
Self-Perceived Eye Comfort			
Same (%)	31.82	83.33	< 0.001
Better (%)	59.09	0.00	
Worse (%)	9.09	16.7	

(Table 5). There were no significant changes in clinical signs for either group when comparing the two-week visits to the baseline visits (Table 5). End-of-day contact lens comfort significantly ($p = 0.045$) improved over the duration of the study for the treatment group while there was no change ($p = 0.64$) in the control group. Wear time was 11.36 \pm 3.61 h, 13.02 \pm 2.61 h, and 12.76 \pm 3.50 h in the artificial tear group while it was 11.45 \pm 3.83 h, 10.81 \pm 3.46 h, and 10.71 \pm 4.74 h in the no treatment group at one day, one week, and two weeks, respectively. Comfortable wear time was 9.56 \pm 4.15 h, 12.38 \pm 3.44 h, and 11.77 \pm 4.13 h in the artificial tear group while it was 8.67 \pm 4.11 h, 9.48 \pm 3.42 h, and 8.51 \pm 4.68 h in the no treatment group at one day, one week, and two weeks, respectively. Wear time ($p = 0.94$) and comfortable wear time ($p = 0.47$) were not significantly different between groups after one day's worth of treatment. Wear time was significantly longer in the artificial tear group when comparing the two groups at one week ($p = 0.02$) but not at two weeks ($p = 0.11$). Comfortable wear time was significantly longer in the artificial tear group at one week ($p = 0.006$) and two weeks ($p = 0.02$) when compared to the no treatment group.

4. Discussion

Practitioners routinely use topical rewetting drops as a first-line treatment to alleviate dryness and discomfort symptoms in contact lens

wearers [23,24]. In fact, apart from a contact lens refit, reduced contact lens wearing time, or prescribing an alternative contact lens disinfection system, rewetting drops are the customary treatment plan for contact lens users with ocular discomfort [24–28]. In addition to dryness being an irritant to the patient, the consequences of discomfort for the care of the patients, the practitioner's practice, and the contact lens industry are premature contact lens removal and complete discontinuation of contact lens wear [29]. Discontinuation of contact lens wear because of discomfort is a real problem with approximately half of all habitual contact lens wearers permanently discontinuing contact lens wear primary because of discomfort [1,3,30,31]. This startling statistic suggests that current rewetting drops are not enough and that there is a need for alternative contact lens discomfort treatment methods. The current study suggests that the application of Systane Complete before and after contact lens use may be one effective alternative for improving contact lens discomfort in symptomatic daily disposable contact lens wearers.

Rewetting drops and artificial tear formulations attempt to stabilize the tear film and replenish tear film volume [18]. These drop formulations vary widely in ionic composition, osmolarity, viscosity, metabolites, compatible solutes, and preservatives [7,11,18]. Some ingredients such as preservatives, paradoxically, can exacerbate ocular surface disorders [11]. This is highlighted by how it has long been recognized that elimination of benzalkonium chloride (preservative) is

Table 5
Outcome Clinical Characteristics Compared to Baseline by Study Group (Worse Eye).

Characteristic	Treatment Group: Systane Complete (P-Value)	Treatment Group: Difference Between Visits (Difference)	Control Group: No Treatment (P-Value)	Control Group: Difference Between Visits (Difference)
Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8)	< 0.0001	7.55 \pm 4.96	0.26	1.00 \pm 4.11
Contact Lens Dry Eye Questionnaire-4 (CLDEQ-4)	< 0.0001	3.77 \pm 2.65	0.56	0.25 \pm 2.42
Standardized Patient Evaluation of Eye Dryness (SPEED)	< 0.0001	2.72 \pm 2.86	1.00	0.38 \pm 3.66
Visual Acuity (logMAR)	0.26	−0.04 \pm 0.19	0.038	0.08 \pm 0.20
Mean Sodium Fluorescein Tear Break Up Time (seconds)	0.28	−0.87 \pm 3.80	0.71	−0.30 \pm 5.18
Corneal Staining (Brien Holden Vision Institute Grading Scale)				
Extent (0-20 scale)	0.75	0.32 \pm 2.55	0.67	−0.13 \pm 2.42
Depth (0-20 scale)	0.21	0.32 \pm 1.21	0.85	−0.13 \pm 1.48
Type (0-20 scale)	0.21	0.32 \pm 1.21	0.93	0.00 \pm 1.29
Schirmer's Test (mm)	0.90	0.27 \pm 9.74	0.17	2.65 \pm 7.91
Meibum Quality – Upper Eyelid (0-4 scale)	0.12	0.45 \pm 1.14	0.81	0.08 \pm 1.72
Meibum Quality – Lower Eyelid (0-4 scale)	0.18	0.45 \pm 1.34	0.71	0.17 \pm 1.31
Meibum Expressibility – Upper Eyelid (0-3 scale)	0.77	0.14 \pm 1.21	0.49	−0.13 \pm 0.99
Meibum Expressibility – Lower Eyelid (0-3 scale)	0.68	0.14 \pm 1.08	1.00	0.08 \pm 0.97

important in the long term safety and tolerability of topical ocular drop preparations [32]. Similarly, careful selection of a comfort drop that mitigates the cause of a patient's underlying symptoms is critical. Since it is well known that there are two primary types of dry eye, aqueous deficient or evaporative dry eye, this should be considered when addressing dryness and discomfort symptoms in contact lens wearers [33]. This is particularly important because the act of wearing a contact lenses alone is likely to deplete tear film (aqueous deficient) components and destabilize (evaporative) the tear film by bisecting the tear film into pre- and post-lens tear layers [34,35]. Systane Ultra is an artificial tear indicated for aqueous deficient dry eye [7]. Systane Ultra is composed of polyethylene glycol 400 (0.4%) and propylene glycol (0.3%) as demulcents and hydroxypropyl guar as a gelling agent [7]. Systane Balance (Alcon, Fort Worth, TX) is an anionic-based phosphatidylglycerol emulsion that is indicated for patients who have meibomian gland dysfunction and evaporative dry eye [6,13,36]. Both Systane Balance and Systane Ultra are preserved with polyquaternium-1, and they have both been found to be safe and effective at treating contact lens discomfort [7,13]. This study attempted to gain an initial understanding of the safety and effectiveness of a new artificial tear's (Systane Complete) ability to treat contact lens discomfort, an artificial tear that combines elements from both Systane Balance and Systane Ultra.

The current study found that subjects who were randomized to use Systane Complete pre-lens-insertion and post-lens-removal (twice a day) had significantly better CLDEQ-8 and CLDEQ-4 scores, respectively, compared to the no treatment group at two weeks. Better CLDEQ-8 scores suggest that the artificial tear group had a global improvement in overall contact lens symptoms and the need to cope for symptoms while better CLDEQ-4 scores suggests an improved unidimensional contact lens dryness/discomfort trait [17,37,38]. Furthermore, the authors believe that the between-groups difference of 3.77 ± 2.65 at two weeks in CLDEQ-4 scores is clinically important, as this difference was highly significant and approximately equal to our original estimate of a clinically meaningful change (4-units) in CLDEQ-4 scores. Nevertheless, a formal clinical study is still needed to establish a true clinically meaningful difference in CLDEQ-4 scores. A significant improvement in comfort is supported by subjects in the artificial tears group who subjectively claimed that their eyes felt better at the two-week mark and by subjects in the artificial tear group who reported longer comfortable wear times and better end-of-day contact lens comfort scores at two weeks compared to the no treatment group. Relatedly, 5 subjects in the artificial group had ocular allergies, which was significantly more common than the no treatment group. While ocular allergies were not controlled for during analysis, it is unlikely that these subjects significantly affected the primary outcomes of this study. If anything, more subjects with ocular allergies in the artificial group would have lessened the significant effect between study groups (more allergy symptoms in the artificial group would have resulted in smaller differences between the artificial tear and no treatment groups). These data overall suggest that using Systane Complete before and after contact lens use is effective at improving subjective contact lens comfort.

Interestingly, subjects in the artificial tear group did not demonstrate significantly better SPEED scores at two weeks compared to the no treatment group. This discrepancy between CLDEQ-8 and SPEED scores could possibly be explained by CLDEQ-8 scores being more reflective of contact lens comfort and SPEED scores being more reflective of dryness symptoms [17]. Alternatively, since CLDEQ-8, CLDEQ-4, and SPEED scores all significantly improved in the artificial tear group at two weeks compared to baseline, yet the no treatment group failed to show an improvement in any of these metrics, there is a chance that the non-significant trend towards better SPEED scores in the artificial tears group compared to the no treatment group at two weeks could have been dampened by the artificial tear group knowing that they were being treated and the no treatment group knowing that they were not

being treated.

This study also found that wear times and comfortable wear times differed throughout the study. This study specifically found that simply being in this study resulted in subjects in both groups wearing their contact lenses on average for more hours per day even after being in the study for just one day (increased from about 8 hours–11 hours per day). This may have occurred because the study doctors encouraged the subjects to wear their contact lenses every day of the study. Nevertheless, wear time itself did not differ between baseline and two weeks for either study group. Interestingly, subjects in the artificial tear group did have an increase in comfortable wear times (about 2 h/day) at one and two weeks compared to baseline, a difference that was significantly better than the no treatment group, which did not have a clinically meaningful change in comfortable wear time during the course of this study.

The patient's perception of dryness can be the results of many mechanisms. The cornea is not known to have nerve receptors for dryness or wetness [39]. As such, a combination of receptor stimuli from the eyelids, cornea, and conjunctiva, together may act to alert the patient and deliver the subjective complaint and feeling. For example, surface lens dehydration could cause the eyelids to aberrantly rub over a "dry lens" in a way that stimulates eyelid margin nerve endings to be interpreted as "dryness". Similarly, it has been suggested that patients use dryness as a complaint that really is derived from the lens-eyelid interaction in a parallel fashion to feelings of dry mouth and is the result of increased friction in this interface [39,40]. The root cause of this condition is likely multifactorial, and it could be the result of any of the following issues: lens edge sensation, soiled lenses, dehydrated lens surface, tear evaporation, altered blink patterns, lens movement, and/or destabilized pre-lens tear layer [24,39]. Data from this study suggests that while tear film deficiencies may promote contact lens discomfort, additional factors such as eyelid interaction with the contact lens may be a more important factor leading to contact lens discomfort. Subjects in the artificial tear group had improved symptoms when using artificial tears compared to baseline compared to the no treatment group at two weeks, yet there were no significant differences in any of the ocular signs (e.g., tear break up time, Schirmer's I test) tested in this study when compared to baseline or the no treatment group at two weeks. Thus, the mechanism by which Systane Complete promotes better contact lens comfort may be more related to reducing ocular friction between the eye and the contact lens [7].

The primary strengths of this study include that all investigators were masked to the subject's group, subjects were randomly allocated to their group, subject compliance with the treatment was high, all enrolled subjects fully completed the study, and only daily disposable soft contact lens wearers were included to avoid any potential confounders from contact lens care systems. One potential limitation to this study was that the enrolled subjects were not fully masked to their treatment group. Specifically, subjects were aware of if they were in the artificial tears group or the no treatment group, and knowledge of being treated or not could potentially have affected the subject's responses when completing the symptoms questionnaires. This knowledge could have subsequently resulted in a placebo effect in the artificial tear group, which may have produced the significant between group differences in contact lens comfort scores and the improvement in contact lens comfort scores in the artificial tear group at two weeks compared to baseline. Although this is possible, the effect seen at two weeks compared to baseline in the artificial tear group is large and highly significant and there was a significant difference between groups at two weeks. Furthermore, one might note that the lack of change in signs is evidence of a placebo effect. Nevertheless, it is not uncommon to find a disconnect between ocular signs and symptoms [41–43], and a lack of change in signs over the course of the study may have simply been due to primarily including patients with on average normal ocular signs. With that said, all subjects were masked to the nature of the study drop (all bottle identifiers were removed), and this experiment followed the

general study design followed by other investigators [7]. Nevertheless, a future study is needed to compare the effectiveness of Systane Complete to an established artificial tear or rewetting drop to determine if Systane Complete is superior to other marketed drops for the treatment of Contact Lens Discomfort or contact lens-related dry eye.

This study overall found that Systane Complete was able to significantly improve contact lens comfort at two weeks compared to baseline and compared to no treatment by simply applying one drop of Systane Complete to each eye before and after contact lens use. Improvements in contact lens comfort are key to maintaining safe and continuous long-term contact lens wear. While the results of this study are still preliminary, additional work to test on-eye direct application of Systane Complete to contact lenses is needed to determine if direct application of artificial tears is safe and potentially more effective than just using artificial tears before and after contact lens use. Until that analysis is completed practitioners can confidently recommend Systane Complete to be used pre-lens insertion (beginning of day) and post-lens removal (end-of-day) for the treatment of Contact Lens Discomfort.

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