

ORIGINAL ARTICLE

OPEN

Dual-Polymer Drops, Contact Lens Comfort, and Lid Wiper Epitheliopathy

Jason J. Nichols*, Christopher W. Lievens†, Marc R. Bloomenstein‡, Haixia Liu§, Peter Simmons§, and Joseph Vehige||

ABSTRACT

Purpose. This study compared a new contact lens rewetting drop containing both carboxymethylcellulose and hyaluronic acid (CMC-HA) with a standard drop containing carboxymethylcellulose only (CMC). Symptoms of discomfort typical in lens wear and lid wiper epitheliopathy (LWE) were assessed over a 3-month period in a diverse sample of contact lens wearers.

Methods. Adapted daily-wear contact lens subjects using hydrogel, silicone hydrogel, or rigid gas permeable lenses were enrolled in this prospective, randomized, double-masked, parallel-group, 90-day study conducted at 15 clinical sites. Subjects were randomized 2:1 to CMC-HA ($n = 244$) or CMC alone ($n = 121$) with dosage at least four times per day, along with their habitual lens care system. At baseline and at days 7, 30, 60, and 90, subject-completed questionnaires, bulbar conjunctival staining, LWE, contact lens distance visual acuity (CLDVA), and standard safety measures were assessed.

Results. At day 90, CMC-HA performed significantly better than CMC in ocular symptoms including dryness throughout the day ($p = 0.006$), and burning/stinging throughout the day ($p = 0.02$) and at the end of the day ($p < 0.001$). CMC-HA also performed numerically better for dryness at the end of day ($p = 0.06$). LWE staining was improved in the CMC-HA group at day 90 whereas it increased slightly in the CMC alone group, with a significant between-group difference ($p = 0.009$). CMC-HA also demonstrated greater reduction in conjunctival staining compared with CMC alone at day 90 ($p = 0.08$). No differences in CLDVA, contact lens wear time, acceptability, and product use were observed, and safety outcomes were similar between groups.

Conclusions. The addition of HA to a standard CMC rewetting drop improves clinical performance. In this comparison of rewetting drop efficacy in contact lens wearers, LWE was a useful clinical sign for differentiating clinical performance. (Optom Vis Sci 2016;93:979–986)

Key Words: dual-polymer drop, lid wiper epitheliopathy, subject-reported outcomes, contact lens, rewetting drops

Contact lens wear is a convenient and effective option for correcting refractive errors. Estimates indicate that more than 39 million individuals use contact lenses in the United States, with approximately 90% wearing daily soft contact lenses.¹ However, ocular discomfort and dryness are

commonly reported as significant side effects and main reasons for discontinuation.^{2–5} Several factors may contribute to or exacerbate discomfort and dryness symptoms while wearing lenses, such as trapped debris, reduction of tear flow, excessive evaporation on the surface of contact lenses, long periods of wear, and use of certain medications (e.g. contraceptives).^{6–9} Varying effects on tear film quality and ocular surface dryness have been reported with both hard (rigid gas permeable [RGP] materials) and soft (hydrogels and silicone hydrogels) contact lenses.^{10–12} Individuals with dry eye are particularly vulnerable to discomfort and episodes of visual complaints while wearing contact lenses.⁹

Contact lens wear can also affect the accuracy of the tools used in dry eye diagnosis and evaluating severity. For example, conjunctival and corneal staining with lissamine green and fluorescein dyes are key measures in identifying dry eye signs in symptomatic non-contact lens wearers.^{13–15} However, in contact lens wearers, conjunctival staining has been shown to have better specificity

*OD, PhD, FAAO

†OD, MS, FAAO

‡OD, FAAO

§PhD

||OD

School of Optometry, University of Alabama at Birmingham, Birmingham, Alabama (JJN); Southern College of Optometry, Memphis, Tennessee (CWL); Schwartz Laser Eye Center, Scottsdale, Arizona (MRB); and Allergan Clinical Research, Irvine, California (HL, PS, JV).

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

than corneal staining.¹⁶ Water content, composition, density, area coverage and depth, as well as deposition and the length of time of lens wear can affect corneal staining, making the test less robust in contact lens wearers.^{17,18}

Lid wiper epitheliopathy (LWE) is a clinical condition characterized by alteration of the epithelium of the portion of the marginal conjunctiva of the eyelid that wipes the ocular surface, diagnosed by staining with fluorescein or lissamine green dyes.^{19,20} Korb et al. first described the condition in soft contact lens wearers, where 80% of subjects with dry eye symptoms and only 13% of asymptomatic subjects displayed LWE.¹⁹ In two studies of dry eye subjects and asymptomatic control subjects, the frequency of LWE was six times greater in dry eye subjects compared with asymptomatic controls.^{20,21} In a study by Yeniad et al., more LWE was detected in contact lens wearers and subjects with dry eye symptoms but no clinical signs than in control subjects.²² Both symptomatic and asymptomatic contact lens wearers demonstrated signs of LWE, and the authors concluded that the lid wiper may traumatize and increase the sensitivity of the cornea, resulting in symptoms of dry eye in contact lens wearers without significant clinical signs (i.e. reduced tear break-up time, low Schirmer's score, or significant fluorescein corneal staining).²²

Rewetting drops are typically used to hydrate and lubricate contact lenses and the ocular surface before and during contact lens wear, as well as preventing drying by stabilizing the tear film and reducing surface tension.²³ Over the past 5 years, a number of topical lubricating formulations containing a variety of ingredients, including polyethylene glycol 400 0.4% and propylene glycol 0.3%,^{24,25} biopolymer tamarind seed polysaccharide-hyaluronic acid,²⁶ and azithromycin ophthalmic solution 1.0%,²⁷ have been studied for alleviating dryness and discomfort associated with contact lens wear. Development of new lubricating drop formulations has evolved with better understanding of the roles of tears and tear film osmolarity, and the involvement of ocular surface inflammation.^{28–31} Recently, a combination of carboxymethylcellulose (CMC) 0.5% and hyaluronic acid (HA) 0.1% was introduced for treatment of dry eye.³² Because CMC and HA polymers readily bind to ocular surface cells,^{33–35} the new formulation was designed to stabilize the tear film and effectively lubricate and protect the ocular surface.

The purpose of this study was to evaluate clinical response to the new CMC-HA eye drop formulation in contact lens wearers with the thought that the HA component would show subjective and clinical benefit.

METHODS

Study Design and Subjects

This was a multicenter, double-masked, randomized, two-arm, parallel-group, 90-day study (ClinicalTrials.gov identifier: NCT01844388) conducted per US Food and Drug Administration (FDA) 510(K) requirement from May to December 2013, at 15 sites in the United States. The study was carried out in accordance with International Conference on Harmonisation Good Clinical Practice and International Organization for Standardization 14155:2011 (Clinical investigation of medical devices for human subjects—good clinical practice) guidelines. Institutional Review

Board (IRB) approval was obtained by each investigator and all subjects provided written informed consent before initiating any study procedures.

Subjects were recruited via IRB-approved emails, office flyers, and newspaper advertisements. Adapted daily-wear contact lens subjects, 18 years of age or older, using one of six types of FDA-approved contact lenses (Vistakon Acuvue 2; Bausch & Lomb PureVision; Ciba Vision Air Optix; Vistakon Acuvue Oasys; CooperVision Biofinity; Bausch & Lomb Boston EO, XO, Menicon Z, or equivalent RGP material) were eligible for enrollment. Subjects used an approved lens care system appropriate for insertion, cleaning, and disinfection of the specific type of contact lenses they were wearing, and did not change care systems during the study. Subjects were excluded if they had recent ophthalmic surgery, were using a topical ocular medication other than rewetting drops, or had any ocular or systemic condition that the investigator deemed might interfere with study results or subject participation in the study. Female subjects of childbearing potential and pregnant subjects were allowed to enroll if they met all inclusion/exclusion criteria and agreed to be followed throughout the term of their pregnancy.

Study Visits and Treatment

The following six study visits were scheduled: screening (1–14 days before baseline), baseline (day 1), and days 7, 30, 60, and 90 follow-up visits. At the baseline visit in each contact lens group, subjects were randomized 2:1 to receive treatment with CMC-HA (Optive Fusion; Allergan plc, Dublin, Ireland) or CMC (Refresh Contacts; Allergan plc). Subjects were instructed to use one to two drops of the study drops in each eye a minimum of four times per day, with one use allowed for preparation of the contact lens by placing one or two drops onto the lens before insertion.

Outcome Measures

Ocular symptoms associated with contact lens wear were graded on a visual analog scale ranging from 0 (none) to 100 (maximum). The extent of burning/stinging, grittiness/foreign body sensation, dryness, difficult/uncomfortable vision, light sensitivity, and overall ocular pain/discomfort symptoms was assessed for throughout the day and at the end of the day.

Conjunctival staining and LWE were measured in each eye utilizing lissamine green stain following the Oxford Scheme for the bulbar conjunctiva¹³ and the method described by Korb et al. for LWE.²¹ Briefly, lissamine green was instilled and staining was evaluated using white light of low-to-moderate intensity (with a diffuser for LWE observation). Conjunctival staining represented by punctate dots was assessed immediately and the sum of nasal and temporal zones graded on a scale of 0 (no dry eye) to 5 (severe dry eye) for each was used as the score for each eye. For LWE assessment, the upper eye lid was everted, carefully avoiding contact with the region of the lid wiper. Individual scores for the horizontal length involved graded from 0 (<2 mm) to 3 (>10 mm) and the sagittal height involved graded from 0 (<25%) to 3 (>75%) were averaged for a final lid wiper staining grade for each eye.

Additional efficacy measures included contact lens distance visual acuity and contact lens wearing time. Safety was assessed by adverse events monitoring, biomicroscopy (including corneal

staining), and reporting of symptoms, problems, and complaints. Study product acceptability and usage were evaluated at each study visit by the Contact Lens Wearing Questionnaire (assessing the subject's contact lens replacement, wearing time, and ocular symptoms associated with contact lens wear), the Study Product Experience Questionnaire (evaluating the subjective experience with the study eye drops in comfort, vision, and tolerability associated with contact lens wear), and the Study Product Usage Questionnaire (reporting the subject's average number of times and how often each day they instilled the study product over the past week and when they last used the study product).

Data Analysis and Statistical Methods

The analysis sample consisted of all randomized subjects. For ocular symptoms, the analysis of variance model with fixed effects of treatment and contact lens type was used for between-group comparisons and paired *t*-tests were used for within-group comparisons of change from baseline. For conjunctival staining and LWE, baseline and change from baseline at each visit were analyzed as continuous variables for the worse eye at baseline using parametric or nonparametric methods. Post hoc analyses were conducted of all subjects in both the CMC-HA and CMC alone groups combined to assess relationships between LWE severity grade and subject-reported ocular symptoms at baseline. Additional

analyses were performed evaluating LWE severity grade among contact lens types in all subjects or within the CMC-HA and CMC treatment groups.

For other efficacy measures, continuous variables were analyzed using either parametric or nonparametric methods and nominal variables were analyzed using the Cochran–Mantel–Haenszel general association test stratified by contact lens type for between-group comparisons. Adverse events were summarized and tabulated for each treatment group. For all analyses performed, $p < 0.05$ was considered to be statistically significant.

RESULTS

Subjects and Baseline Characteristics

A total of 365 subjects were enrolled (244 subjects in the CMC-HA group; 121 subjects in the CMC alone group). Overall, 15 subjects (8 [3.3%] CMC-HA, 7 [5.8%] CMC alone) did not complete the study due to personal reasons (6 [1.6%]), adverse events (3 [0.8%]), lost to follow-up (3 [0.8%]), protocol violation (1 [0.3%]), and other reasons (2 [0.5%]). Baseline demographics and ocular histories were similar between the CMC-HA and CMC alone treatment groups (Table 1). The mean (SD) age of subjects enrolled in the study was 34.5 (10.8) years and the majority were Caucasian (85.5%) and female (74.5%).

TABLE 1.

Subjects' demographics and characteristics at baseline (intent-to-treat population)

Characteristic, n (%)	CMC-HA (n = 244)	CMC (n = 121)	Total (N = 365)	p-value*
Mean (SD) age, yr	34.9 (11.1)	33.7 (10.3)	34.5 (10.8)	0.305
Range	18–78	18–68	18–78	
<40	170 (69.7)	90 (74.4)	260 (71.2)	
≥40	74 (30.3)	31 (25.6)	105 (28.8)	
Sex				0.965
Female	182 (74.6)	90 (74.4)	272 (74.5)	
Male	62 (25.4)	31 (25.6)	93 (25.5)	
Race				0.652†
Caucasian	210 (86.1)	102 (84.3)	312 (85.5)	
Asian	13 (5.3)	6 (5.0)	19 (5.2)	
Black	12 (4.9)	4 (3.3)	16 (4.4)	
Hispanic	5 (2.0)	6 (5.0)	11 (3.0)	
Other	4 (1.6)	3 (2.5)	7 (1.9)	
Ophthalmic history‡				—
Dry eye	23 (9.4)	14 (11.6)	37 (10.1)	
Vitreous floaters	18 (7.4)	7 (5.8)	25 (6.8)	
Conjunctivitis	10 (4.1)	7 (5.8)	17 (4.7)	
Ulcerative keratitis	6 (2.5)	3 (2.5)	9 (2.5)	
Cataract	6 (2.5)	1 (0.8)	7 (1.9)	
Conjunctival staining score, mean (SD)	2.0 (1.6)	1.9 (1.6)	—	0.448
Lid wiper epitheliopathy grade, mean (SD)	0.7 (0.8)	0.5 (0.7)	—	0.042

*p-values for CMC-HA versus CMC alone based on one-way analysis of variance (ANOVA) model for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables; ANOVA model with fixed effects of treatment and stratification factor of contact lens type, and the Type III sum of squares used for conjunctival staining and lid wiper epitheliopathy grade comparisons.

†Caucasian versus non-Caucasian.

‡Ophthalmic event or condition reported before study entry occurring in ≥2.5% of subjects in either treatment group; between group analyses were not performed.

CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid; SD, standard deviation.

TABLE 2.

Change from baseline in ocular symptoms at day 90 after treatment with CMC-HA and CMC alone

Ocular symptom	Mean \pm SD change from baseline (p-value*)		Between-group difference (p-value†)
	CMC-HA (n = 244)	CMC alone (n = 121)	
Throughout the day			
Burning/stinging	-1.8 \pm 11.9 (0.02)	1.2 \pm 11.4 (0.27)	-3.10 (0.02)
Grittiness/foreign body sensation	-3.1 \pm 13.3 (<0.001)	-2.1 \pm 13.3 (0.10)	-1.26 (0.40)
Dryness	-9.3 \pm 17.6 (<0.001)	-3.3 \pm 21.5 (0.10)	-5.98 (0.006)
Difficult/uncomfortable vision	-2.1 \pm 13.7 (0.02)	-2.7 \pm 13.1 (0.03)	0.65 (0.68)
Light sensitivity	-3.1 \pm 15.1 (0.002)	-2.0 \pm 12.8 (0.09)	-0.90 (0.58)
Overall ocular pain/discomfort	-1.6 \pm 10.4 (0.02)	-0.3 \pm 12.3 (0.79)	-1.31 (0.30)
End of the day			
Burning/stinging	-6.2 \pm 16.0 (<0.001)	0.2 \pm 16.4 (0.90)	-6.57 (<0.001)
Grittiness/foreign body sensation	-6.4 \pm 20.9 (<0.001)	-4.8 \pm 20.1 (0.01)	-1.89 (0.42)
Dryness	-17.9 \pm 26.4 (<0.001)	-11.7 \pm 30.5 (<0.001)	-6.14 (0.06)
Difficult/uncomfortable vision	-7.6 \pm 22.1 (<0.001)	-4.5 \pm 22.1 (0.03)	-3.15 (0.21)
Light sensitivity	-2.8 \pm 15.6 (0.006)	-1.6 \pm 15.7 (0.28)	-1.10 (0.54)
Overall ocular pain/discomfort	-6.1 \pm 19.7 (<0.001)	-2.9 \pm 21.1 (0.15)	-3.29 (0.16)

*Paired *t*-test; bold font indicates significant change from baseline.

†Analysis of variance model with fixed effects of treatment and stratification factor of contact lens type, and the Type III sum of squares; bold font indicates significant difference between CMC-HA and CMC alone.

CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid.

Ocular Symptoms

At day 90, subjects in the CMC-HA group reported significant improvements for all ocular symptoms throughout the day and at the end of the day ($p \leq 0.02$; Table 2). In the CMC alone group, there was a significant improvement in difficult/uncomfortable vision throughout the day, as well as grittiness/foreign body sensation, dryness, and difficult/uncomfortable vision at the end of the day ($p \leq 0.03$; Table 2). For comparison between the two treatment groups, burning/stinging throughout the day (-1.8 vs. 1.2 ; $p = 0.02$) and at the end of the day (-6.2 vs. 0.2 ; $p < 0.001$) and dryness throughout the day (-9.3 vs. -3.3 ; $p = 0.006$) were significantly improved (lower scores), and dryness at the end of the day (-17.9 vs. -11.7 ; $p = 0.06$) was directionally more improved in the CMC-HA group compared with the CMC alone group at day 90, respectively (Fig. 1, Table 2).

Conjunctival Staining

For bulbar conjunctival staining, analysis of change from baseline of the worse eye at baseline demonstrated decreasing severity in both the CMC-HA and CMC alone treatment groups. Greater reduction in conjunctival staining was observed with CMC-HA than CMC at day 90 (mean [SD]: -0.33 [1.6] vs. -0.03 [1.4]; $p = 0.08$) (Fig. 2).

Lid Wiper Epitheliopathy

LWE staining grades were significantly higher at baseline in the CMC-HA group than the CMC alone group (mean [SD] 0.7 [0.8] vs. 0.5 [0.7]; $p = 0.04$). Analysis of the worse eye at baseline showed that mean (SD) LWE grade decreased in the CMC-HA group (-0.13 [0.8]) but slightly increased in the CMC alone group (0.1 [0.8]) by day 90 (between-group difference: -0.23 ; $p = 0.009$) (Fig. 3). A post hoc exploratory analysis suggested that higher baseline LWE staining grades were correlated with greater grittiness/foreign

body sensation, dryness, ocular pain/discomfort, and light sensitivity symptoms scores throughout the day and at the end of the day (correlation coefficient [*r*] range: 0.62 – 0.75 ; $p = 0.05$ – 0.14), although correlations did not reach statistical significance. In contrast, baseline LWE staining grades did not appear to be correlated with burning/stinging and difficult/uncomfortable vision symptoms scores (*r* range: 0.03 – 0.43 ; $p = 0.34$ – 0.95) (Table 3).

At baseline, in all subjects regardless of treatment group, there were no significant differences in LWE staining grade by lens type ($p = 0.82$) and no significant differences were observed within the CMC-HA ($p = 0.60$) or CMC alone ($p = 0.52$) treatment groups among contact lens types. Analysis at follow-up visits revealed that within the CMC-HA group, significant differences in the change from baseline in LWE staining grade were observed in favor of Acuvue 2 compared with PureVision ($p = 0.01$), Acuvue Oasys ($p = 0.01$), Biofinity ($p = 0.02$), and Boston EO, XO, Menicon Z, or equivalent ($p = 0.03$) lenses at day 30. There were no statistically significant differences between contact lens type at the end of the study/day 90 in the CMC-HA group, although a trend towards significance was observed with Acuvue 2 compared with PureVision ($p = 0.05$) (Table 4). Within the CMC alone group, significant differences in the change from baseline in LWE staining grade were observed in favor of Boston EO, XO, Menicon Z, or equivalent contact lenses compared with Acuvue Oasys and Air Optix ($p = 0.03$ for both) at day 30. Significant or directional differences were still observed in favor of Boston EO, XO, Menicon Z, or equivalent lenses compared with Air Optix ($p = 0.005$) and Acuvue Oasys ($p = 0.06$) lenses at day 90. Acuvue 2 lenses were also observed to be significantly better than Air Optix ($p = 0.008$) at day 90 in the CMC alone group (Table 4).

Other Efficacy Assessments

No differences were observed between CMC-HA and CMC alone groups in contact lens distance visual acuity at day 90

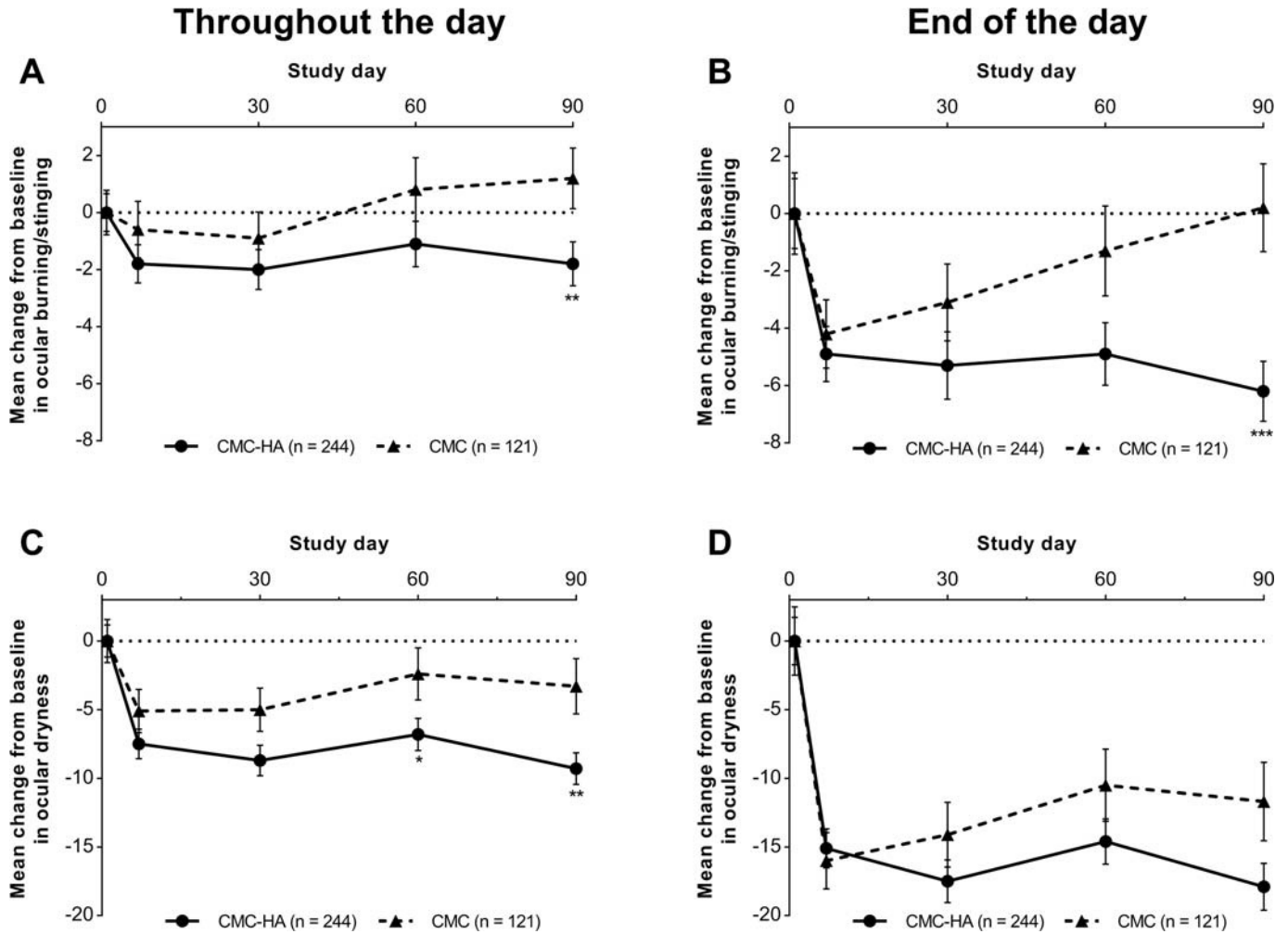


FIGURE 1. Mean change from baseline in burning/stinging (A, B) and dryness (C, D) ocular symptoms, assessed throughout the day and at the end of day at each follow-up visit. Error bars represent standard error of the mean. * $p < 0.05$, ** $p \leq 0.02$, *** $p < 0.001$ based on analysis of variance model with fixed effects of treatment and stratification factor of lens type, and the Type III sum of squares. CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid.

(subjects with better ≥ 2 -line increase] or no change [-2 to $+2$ line change] in visual acuity: 90% vs. 89.1%; $p = 0.76$) and in categories of change in the number of lines read (subjects with ≥ 1 line of vision gained: 47.2% vs. 50.4%, respectively). The mean (SD)

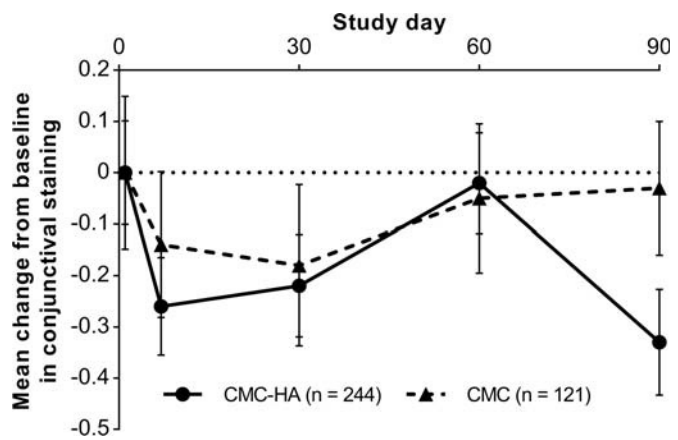


FIGURE 2. Mean change from baseline at each follow-up visit in bulbar conjunctival staining in the worse eye at baseline. Error bars represent standard error of the mean. CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid.

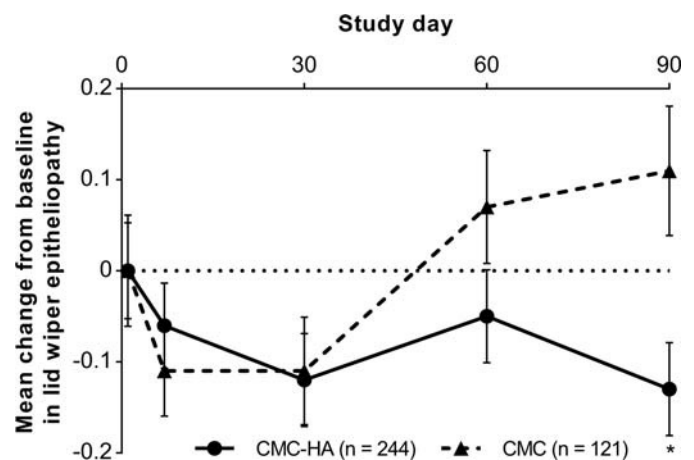


FIGURE 3. Mean change from baseline at each follow-up visit in LWE severity grade in the worse eye at baseline. Error bars indicate standard error of the mean. * $p = 0.009$ based on analysis of variance model with fixed effects of treatment and stratification factor of lens type, and the Type III sum of squares. LWE, lid wiper epitheliopathy; CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid.

TABLE 3.

Correlation between LWE staining scores and median subject-reported ocular symptoms scores at baseline

Ocular symptom	Correlation between LWE and ocular symptoms Correlation coefficient <i>r</i> (p-value)*	
	Throughout the day	End of the day
Burning/stinging	0.35 (0.44)	0.43 (0.34)
Grittiness/foreign body sensation	0.75 (0.05)	0.70 (0.08)
Dryness	0.68 (0.10)	0.74 (0.06)
Difficult/uncomfortable vision	0.03 (0.95)	0.15 (0.75)
Light sensitivity	0.69 (0.09)	0.62 (0.14)
Overall ocular pain/discomfort	0.70 (0.08)	0.68 (0.09)

*Bold font indicates greater correlation between LWE staining score and ocular symptoms score at baseline.

LWE, lid wiper epitheliopathy.

change in hours per day (−0.1 [2.7] vs. −0.2 [2.9]; *p* = 0.69) and number of days (0.4 [3.1] vs. 0.3 [3.1]; *p* = 0.94) lenses were worn in the previous week, as well as the hours per day lenses were worn comfortably (0.1 [0.7] vs. 0.1 [0.7]; *p* = 0.68) in the previous week were similar between the CMC-HA and CMC alone treatment

TABLE 4.

Paired comparison of change from baseline in LWE severity between contact lens type at 30- and 90-day follow-up visits*

Treatment group	Mean rank difference (p-value) between contact lens type at day 30†				
CMC-HA	Acuvue Oasys	Air Optix	Biofinity	PureVision	Boston EO, XO
Acuvue 2	−34.74 (0.01)	−16.54 (0.24)	−33.57 (0.02)	−35.93 (0.01)	−31.67 (0.03)
Acuvue Oasys		18.20 (0.20)	1.17 (0.93)	−1.19 (0.93)	3.08 (0.83)
Air Optix			−17.03 (0.23)	−19.39 (0.17)	−15.12 (0.29)
Biofinity				−2.36 (0.87)	1.90 (0.89)
PureVision					−4.26 (0.77)
CMC	Acuvue Oasys	Air Optix	Biofinity	PureVision	Boston EO, XO
Acuvue 2	−10.05 (0.28)	−10.07 (0.28)	0.93 (0.92)	−4.00 (0.66)	11.59 (0.22)
Acuvue Oasys		−0.03 (>0.99)	10.98 (0.26)	6.05 (0.52)	21.63 (0.03)
Air Optix			11.00 (0.26)	6.07 (0.52)	21.66 (0.03)
Biofinity				−4.93 (0.61)	10.66 (0.28)
PureVision					−15.59 (0.10)
Treatment group	Mean rank difference (p-value) between contact lens type at day 90†				
CMC-HA	Acuvue Oasys	Air Optix	Biofinity	PureVision	Boston EO, XO
Acuvue 2	−20.85 (0.14)	−6.67 (0.63)	−12.39 (0.37)	−27.40 (0.05)	−22.78 (0.11)
Acuvue Oasys		14.19 (0.32)	8.47 (0.55)	−6.55 (0.65)	−1.93 (0.90)
Air Optix			−5.72 (0.68)	−20.73 (0.15)	−16.11 (0.27)
Biofinity				−15.01 (0.29)	−10.39 (0.47)
PureVision					−4.62 (0.75)
CMC	Acuvue Oasys	Air Optix	Biofinity	PureVision	Boston EO, XO
Acuvue 2	−16.55 (0.09)	−26.23 (0.008)	−9.15 (0.36)	−14.12 (0.14)	2.34 (0.81)
Acuvue Oasys		−9.67 (0.33)	7.40 (0.46)	2.44 (0.80)	18.89 (0.06)
Air Optix			17.07 (0.10)	12.11 (0.21)	28.57 (0.005)
Biofinity				−4.97 (0.61)	11.49 (0.25)
PureVision					−16.46 (0.09)

*Vistakon Acuvue 2; Bausch & Lomb PureVision; Ciba Vision Air Optix; Vistakon Acuvue Oasys; CooperVision Biofinity; Bausch & Lomb Boston EO, XO, Menicon Z, or equivalent rigid gas permeable material.

†*p*-values for between-contact lens comparisons based on ANCOVA model on the rank of the change from baseline with contact lens strata as a factor; mean rank differences from the least square means based on the same ANCOVA model; negative mean rank difference indicates difference in favor of the contact lens type in the left column being compared with the lens type in the top row, positive mean rank difference indicates difference in favor of the contact lens type in the top row being compared to the lens type in the left column. Bold font indicates significant difference between contact lens types.

LWE, lid wiper epitheliopathy; CMC, 0.5% carboxymethylcellulose; HA, 0.1% hyaluronic acid; ANCOVA, analysis of covariance.

groups, respectively. General acceptability results showed no differences between CMC-HA and CMC alone in any of the 10 questions of lens comfort and fit, overall eye comfort, quality of vision, and preference with the products at any study visit. The number of times per day that the study product was used during the week before the day 90 visit was the same for CMC-HA and CMC alone treatment groups (mean [SD] 4.5 [1.1] vs. 4.4 [0.7]; *p* = 0.49).

Adverse Events

Ocular adverse events were reported in similar proportions of subjects in the CMC-HA group (17 [7.0%]) and CMC alone group (8 [6.6%]; *p* = 0.90). Treatment-related adverse events were reported in 10 subjects (4.1%) in the CMC-HA group and 5 subjects (4.1%) in the CMC alone treatment group (*p* > 0.99). The most common treatment-related adverse events reported in either the CMC-HA group or CMC alone group were conjunctival staining (2.9% vs. 1.7%), blurred vision (1.2% vs. 0.8%), dry eye (0.8% vs. 2.5%), and photophobia (0.4% vs. 1.7%). One serious adverse event was reported (spontaneous abortion in the CMC-HA group) and was deemed unrelated to study treatment by the investigator. Of the three subjects who discontinued the study due to adverse events, 2 (0.8%) were in the CMC-HA group and 1 (0.8%) in the CMC alone group.

DISCUSSION

This study demonstrates that the use of a new eye drop containing a combination of CMC and HA during lens wear provides greater improvement in ocular symptoms, and reductions in conjunctival staining and LWE than an existing eye drop containing CMC alone. With regard to ocular comfort, it is notable that the use of CMC-HA resulted in significant reductions ($p \leq 0.02$) in all six measures of ocular symptoms both throughout the day and at the end of the day by the day 90 visit (12 total comparisons). In contrast, the change from baseline symptoms scores for CMC alone was significant in only 4 of the 12 comparisons. In addition, the improvement in symptoms was numerically greater in the CMC-HA group compared with the CMC alone group in 11 of the 12 instances.

Based on analyses of subjects' worse eyes at baseline, conjunctival staining and LWE severity were similar between the treatment groups in early follow-up study visits. By day 90, the CMC-HA treatment group demonstrated improvement in conjunctival staining and significantly better LWE staining grade ($p = 0.009$) compared with the CMC alone treatment group. Although conjunctival and corneal staining are common outcome measures in studies evaluating the efficacy of lubricating eye drops in dry eye, conjunctival staining was a focus in this study, as it has been reported that corneal staining is affected by contact lens-related factors such as water content, composition material, wearing time and deposition, as well as the extent (area of coverage), density, and depth of contact lenses.^{17,18} Subjects enrolled in our study were permitted to wear one of six different FDA-approved soft (hydrogels and silicone hydrogels) and hard (RGP materials) contact lenses, which would have confounded corneal staining results. Corneal staining was assessed as part of the biomicroscopy examination for safety, but due to the above factors, no formal analysis was performed.

Post hoc analysis revealed some associations between LWE severity and subject-reported ocular symptoms at baseline, where higher LWE grades were correlated with more grittiness/foreign body sensation, dryness, overall ocular pain/uncomfortable vision, and light sensitivity scores (correlation coefficient ≈ 0.6 – 0.8) although the correlations did not reach statistical significance. This may be due to limitations of correlation analysis for discrete grading scales such as LWE (there were only seven possible values in the current study).

No strong correlation between LWE severity and burning/stinging was observed. Lin et al. reviewed published literature on mechanical effects of silicone hydrogel contact lenses and surmised that mechanical irritation likely contributes to LWE and other ocular complications including corneal erosions and papillary conjunctivitis.³⁶ Our findings are consistent with this concept that LWE may be a result of mechanical irritation of the lid wiper from the contact lenses rather than a reaction to irritating chemicals on the ocular surface.

In addition, analysis of changes in LWE severity among contact lens type demonstrated that by day 90, improvements in LWE were generally observed in subjects wearing all lens types (group IV hydrogel, silicone hydrogel, or RGP) in the CMC-HA group though subjects wearing Acuvue 2 showed better improvement almost reaching significance ($p = 0.05$) compared with PureVision silicone hydrogel lens wearers. In contrast, subjects wearing RGP

contact lenses demonstrated more significant improvements in LWE compared with those wearing silicone hydrogel lens types, as well as subjects wearing Acuvue 2 lenses compared with Air Optix lenses in the CMC alone group. These findings suggest that perhaps RGP lenses benefit more from reduced mechanical irritation from a lower viscosity eye drop (18 centipoise for CMC-HA vs. 2–4 centipoise for CMC alone; data on file), but further investigations are required to fully elucidate underlying mechanisms.

Lid wiper epitheliopathy has been established as a diagnostic sign of dry eye in subjects with dry eye disease and in contact lens wearers,^{19–22} and LWE severity has been reported to vary depending on lens type.³⁷ To date, there have been no previous studies reported that have specifically investigated the use of rewetting drops and effects on LWE. Although the present study suggests some differences in LWE response in different contact lens types, there was no consistent pattern observed. The previous study by Schulze et al. was a single assessment of LWE in wearers of daily disposable contact lenses,³⁷ which were not investigated in the current study. The overall level of LWE staining in this successful contact lens wearing population was relatively low and the baseline levels of LWE staining were slightly different between groups, so the clinical significance of the present results is limited. Additional studies are warranted to further characterize effects of contact lens types on LWE, and also among patients selected for higher baseline levels of LWE staining, to better characterize the efficacy of rewetting drops in reducing LWE severity in contact lens wearers.

Both CMC-HA and CMC rewetting drops were safe and well tolerated; approximately 4% of subjects discontinued during the course of the study. A similar proportion of subjects withdrew from the study due to adverse events in either treatment group. Overall, results from the present study suggest that regular daily use of a rewetting drop containing both CMC and HA polymers reduces ocular symptoms and associated signs in a wide variety of contact lens wearers. Additionally, results of the LWE evaluation and the relationship between LWE severity and subject-reported ocular symptoms further support the utility of LWE as a tool for diagnosing ocular dryness and monitoring effectiveness of lubricating agents.

ACKNOWLEDGMENTS

This study was sponsored by Allergan plc, Dublin, Ireland. Writing and editorial assistance was provided to the authors by Kakuri M. Omari, PhD, of Evidence Scientific Solutions, Philadelphia, PA, USA, and funded by Allergan plc. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship. The authors would like to thank the following participating investigators who provided and cared for the study subjects: Marc R. Bloomenstein, OD, Scottsdale, AZ; William J. Bogus, OD, Salt Lake City, UT; Mark D. Curtis, OD, Warrensburg, MO; David T. Douglass, OD, Bangor, ME; Kerry A. Giedd, OD, Orlando, FL; Paul J. Hartman, MD, Rochester, NY; Christopher W. Lievens, OD, Memphis, TN; Stephen M. Montaquila, OD, Warwick, RI; Wilson Movic, OD, Bloomington, IL; Jason J. Nichols, OD, Houston, TX; Thomas G. Quinn, OD, Athens, OH; Cheryl Vincent-Riemer, OD, East Lansing, MI; Mary Jo Stiegemeier, OD, Beachwood, OH; Peter Van Hoven, OD, Brentwood, TN; and Eric M. White, OD, San Diego, CA.

JJN has no conflicts of interest to disclose; CWL has served as an advisor to Allergan plc; MRB is a consultant to Allergan plc; HL, PS, and JV are employees of Allergan plc, Irvine, CA.

Received August 31, 2015; accepted January 26, 2016.

REFERENCES

- Nichols JJ. 2014 Annual Report: Contact Lenses 2014. The industry maintained healthy growth in 2014, with some categories poised for strong expansion. *Contact Lens Spectrum* 2015;30:22–7.
- Dumbleton K, Woods CA, Jones LW, Fonn D. The impact of contemporary contact lenses on contact lens discontinuation. *Eye Contact Lens* 2013;39:93–9.
- Richdale K, Sinnott LT, Skadahl E, Nichols JJ. Frequency of and factors associated with contact lens dissatisfaction and discontinuation. *Cornea* 2007;26:168–74.
- Young G, Veys J, Pritchard N, Coleman S. A multi-centre study of lapsed contact lens wearers. *Ophthalmic Physiol Opt* 2002;22:516–27.
- Pritchard N, Fonn D, Brazeau D. Discontinuation of contact lens wear: a survey. *Int Contact Lens Clin* 1999;26:157–62.
- Chalmers R. Overview of factors that affect comfort with modern soft contact lenses. *Cont Lens Anterior Eye* 2014;37:65–76.
- Nichols JJ, Sinnott LT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. *Invest Ophthalmol Vis Sci* 2006;47:1319–28.
- Epidemiology Subcommittee of the International Dry Eye Workshop. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf* 2007;5:93–107.
- Dumbleton K, Caffery B, Dogru M, Hickson-Curran S, Kern J, Kojima T, Morgan PB, Purslow C, Robertson DM, Nelson JD. The TFOS International Workshop on Contact Lens Discomfort: report of the subcommittee on epidemiology. *Invest Ophthalmol Vis Sci* 2013;54:TFOS20–36.
- Tyagi G, Alonso-Caneiro D, Collins M, Read S. Tear film surface quality with rigid and soft contact lenses. *Eye Contact Lens* 2012;38:171–8.
- Young G, Chalmers R, Napier L, Kern J, Hunt C, Dumbleton K. Soft contact lens-related dryness with and without clinical signs. *Optom Vis Sci* 2012;89:1125–32.
- Best N, Drury L, Wolffsohn JS. Predicting success with silicone-hydrogel contact lenses in new wearers. *Cont Lens Anterior Eye* 2013;36:232–7.
- Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003;22:640–50.
- Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT, Dua HS, Hom M, Karpecki PM, Laibson PR, Lemp MA, Meisler DM, Del Castillo JM, O'Brien TP, Pflugfelder SC, Rolando M, Schein OD, Seitz B, Tseng SC, van Setten G, Wilson SE, Yiu SC. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. *Cornea* 2006;25:900–7.
- Management and Therapy Subcommittee of the International Dry Eye Workshop. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf* 2007;5:163–78.
- Guillon M, Maissa C. Bulbar conjunctival staining in contact lens wearers and non lens wearers and its association with symptomatology. *Cont Lens Anterior Eye* 2005;28:67–73.
- Fonn D, Peterson R, Woods C. Corneal staining as a response to contact lens wear. *Eye Contact Lens* 2010;36:318–21.
- Nichols JJ, Sinnott LT. Tear film, contact lens, and patient factors associated with corneal staining. *Invest Ophthalmol Vis Sci* 2011;52:1127–37.
- Korb DR, Greiner JV, Herman JP, Hebert E, Finnemore VM, Exford JM, Glonek T, Olson MC. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. *CLAO J* 2002;28:211–6.
- Korb DR, Herman JP, Greiner JV, Scaffidi RC, Finnemore VM, Exford JM, Blackie CA, Douglass T. Lid wiper epitheliopathy and dry eye symptoms. *Eye Contact Lens* 2005;31:2–8.
- Korb DR, Herman JP, Blackie CA, Scaffidi RC, Greiner JV, Exford JM, Finnemore VM. Prevalence of lid wiper epitheliopathy in subjects with dry eye signs and symptoms. *Cornea* 2010;29:377–83.
- Yeniad B, Beginoglu M, Bilgin LK. Lid-wiper epitheliopathy in contact lens users and patients with dry eye. *Eye Contact Lens* 2010;36:140–3.
- Papas EB, Ciolino JB, Jacobs D, Miller WL, Pult H, Sahin A, Srinivasan S, Tauber J, Wolffsohn JS, Nelson JD. The TFOS International Workshop on Contact Lens Discomfort: report of the management and therapy subcommittee. *Invest Ophthalmol Vis Sci* 2013;54:TFOS183–203.
- Kading D. A two-week clinical evaluation of the safety of Systane Ultra in contact lens-wearing patients. *Clin Ophthalmol* 2010;4:27–32.
- McDonald M, Schachet JL, Lievens CW, Kern JR. Systane® ultra lubricant eye drops for treatment of contact lens-related dryness. *Eye Contact Lens* 2014;40:106–10.
- Versura P, Profazio V, Balducci N, Campos EC. Efficacy of two-month treatment with Xilolai eyedrops for discomfort from disposable soft contact lenses. *Clin Ophthalmol* 2010;4:1035–41.
- Nichols JJ, Bickle KM, Zink RC, Schiewe MD, Haque RM, Nichols KK. Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. *Eye Contact Lens* 2012;38:73–9.
- Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, Akova YA, Geerling G, Labetoulle M, Rolando M. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. *Ocul Surf* 2013;11:246–58.
- Pflugfelder SC, Corrales RM, de Paiva CS. T helper cytokines in dry eye disease. *Exp Eye Res* 2013;117:118–25.
- Stahl U, Willcox M, Stapleton F. Osmolality and tear film dynamics. *Clin Exp Optom* 2012;95:3–11.
- Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. *Arch Ophthalmol* 2012;130:90–100.
- Simmons PA, Liu H, Carlisle-Wilcox C, Vehige JG. Efficacy and safety of two new formulations of artificial tears in subjects with dry eye disease: a 3-month, multicenter, active-controlled, randomized trial. *Clin Ophthalmol* 2015;9:665–75.
- Garrett Q, Simmons PA, Xu S, Vehige J, Zhao Z, Ehrmann K, Willcox M. Carboxymethylcellulose binds to human corneal epithelial cells and is a modulator of corneal epithelial wound healing. *Invest Ophthalmol Vis Sci* 2007;48:1559–67.
- Härfstrand A, Molander N, Stenevi U, Apple D, Schenholm M, Madsen K. Evidence of hyaluronic acid and hyaluronic acid binding sites on human corneal endothelium. *J Cataract Refract Surg* 1992;18:265–9.
- Madsen K, Schenholm M, Jahnke G, Tengblad A. Hyaluronate binding to intact corneas and cultured endothelial cells. *Invest Ophthalmol Vis Sci* 1989;30:2132–7.
- Lin MC, Yeh TN. Mechanical complications induced by silicone hydrogel contact lenses. *Eye Contact Lens* 2013;39:115–24.
- Schulze MM, Luensmann D, Hickson-Curran SB, Toubouti Y, Cox S, Plowright AJ, Nichols JJ, Morgan PB, Jones LW. Analysis of lid wiper epitheliopathy in habitual soft lens wearers. *Optom Vis Sci* 2014;91E-Abstract 140104.

Jason J. Nichols

*School of Optometry
University of Alabama at Birmingham
1716 University Blvd
Birmingham, AL 35233
e-mail: jjn@uab.edu*