Safety and efficacy of a hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop in patients with dry eye

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ABSTRACT

Aims To demonstrate non-inferiority of a hydroxypropyl guar/polyethylene glycol/propylene glycol lubricating eye-drop (HPG/PEG/PG) compared with an osmoprotective carboxymethylcellulose/glycerine eye-drop (O/CMC) for ocular surface staining.

Methods This was a multicentre, randomised, observer-masked, parallel-group study. Adults with dry eye instilled HPG/PEG/PG/ or O/CMC 4 times daily for 35 days and then as needed through day 90. Total ocular surface staining (TOSS) score changes from baseline and Impact of Dry Eye on Everyday Life (IDEEL) treatment satisfaction module scores were assessed. Non-inferiority, based on TOSS score change from baseline, was concluded if the upper limit of the 2-sided CI was <2 units.

Results Mean±SD patient age was 64.4±13.7 years; 94 patients were randomised to treatment (HPG/PEG/PG, n=46; O/CMC, n=48). Mean±SE TOSS score change from baseline to day 35 was −2.2±0.33 with HPG/PEG/PG and −1.7±0.47 with O/CMC (treatment difference, −0.47±0.47; p=0.38), and the non-inferiority criterion was met. IDEEL treatment satisfaction scores were similar between groups at day 35 and day 90. The most frequently reported adverse event was eye irritation (HPG/PEG/PG, n=2; O/CMC, n=3).

Conclusions HPG/PEG/PG and O/CMC reduced ocular surface damage, and HPG/PEG/PG was non-inferior to O/CMC. Both treatments were effective, convenient and well tolerated.

Trial registration number NCT01863368, Results.

INTRODUCTION

Dry eye disease is characterised by disruption of tear film composition and homoeostasis and can lead to ocular surface damage caused by exposure and desiccation of the cornea and conjunctival epithelia, hyperosmolarity of the tear film, and inflammation.[1 2] Common causes include decreased production or increased evaporation of the aqueous component of the tear film.[1] Increased evaporation typically results from lipid deficiency and decreased tear film stability. Estimates of the prevalence of dry eye range from 5% to 35%,[3] although the condition may be underdiagnosed because of the lack of consistent correlation between objective signs (eg, ocular staining, decreased tear film break-up time) and patient-reported symptoms (eg, burning, grittiness).[1 4–6] Untreated, corneal damage induces discomfort and visual disturbances that reduce health-related and vision-related quality of life.[7–9]

The goals of dry eye management include restoring the tear film and preventing or reducing damage to the ocular surface to improve ocular symptoms and quality of vision. Artificial tear formulations are considered first-line treatments for dry eye. Saline eye-drops temporarily replace the aqueous component of the tear film but do not restore or mimic the lipid or mucin components of the tear film and therefore do not promote tear film stability or sustained lubrication and ocular surface protection. Lubricating eye-drops containing lipids, demulcents or polymers are more effective in maintaining hydration and protecting the ocular surface by mimicking the lipid and/or mucin components and improving the aqueous layer due to water retention in the polymer network.[10 11]

Lubricant Eye Drops are formulated with polyethylene glycol (PEG) and propylene glycol (PG) and the mucomimetic agent hydroxypropyl guar (HPG) that provides tensioactive, gelification and lubrication properties. The formulation also contains borate and sorbitol, which compete in the eye-drop bottle to reduce borate-mediated cross-linking of HPG.[11] When the low-viscosity formulation is applied to the ocular surface, the sorbitol is diluted by tears, allowing the borate and divalent ions present in the tear film to interact with HPG. This promotes HPG cross-linking to create a structured polymeric network with bioadhesive properties on the ocular surface that prolongs retention of PEG and PG to increase tear film stability, provide sustained lubrication and protect the ocular surface.[11] The safety and efficacy of formulations containing the active components of Systane Ultra (HPG/PEG/PG) have been demonstrated in dry eye populations.[12–16] In laboratory assessments, HPG/PEG/PG protected corneal epithelial cells from desiccation and decreased tissue surface friction during simulated blinking,[17] indicating that HPG/PEG/PG effectively hydrates and lubricates the ocular surface. Further, in a randomised, double-masked cross-over study of patients with dry eye, HPG/PEG/PG maintained visual acuity for a longer duration between blinks 90 min after instillation compared with a carboxymethylcellulose (CMC)-based eye-drop.[18]

Optive Lubricant Eye Drops contain the water-soluble polymer CMC, which binds to the cell surface to reduce water loss, and osmoprotective agents (glycerine, L-carnitine and erythritol). This osmoprotective formulation (O/CMC) lubricates and protects the ocular surface and promotes epithelial cell growth to protect the ocular surface

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from hypertonic stress associated with increased osmolarity of the tear film.[2 19] In studies of patients with dry eye, treatment with O/CMC decreased ocular staining indicative of epithelial damage, increased tear film stability, and improved patient-reported symptoms and ocular comfort.[16 20–22]

The primary objective of this study was to demonstrate non-inferiority of HPG/PEG/PG compared with O/CMC for ocular surface staining after 35 days of four times a day dosing in patients with predominantly aqueous-deficient dry eye (as opposed to dry eye predominantly characterised by meibomian gland dysfunction).

METHODS

Study design and treatment

This was a 90-day, prospective, randomised, observer-masked, parallel-group study conducted at 16 sites in France and Germany from September 2013 to June 2014 (ClinicalTrials.gov identifier, NCT01863368).

The study included a washout phase and two sequential treatment phases (figure 1). The washout phase consisted of the screening visit and a 7-day to 14-day washout period during which patients discontinued all prior artificial tears and administered preservative-free saline eye-drops (one drop in both eyes four times a day). In the first treatment phase, patients completed a postwashout baseline visit (day 0) and were randomised to receive either HPG/PEG/PG (Systane Ultra Lubricant Eye Drops preserved with polyquaternium-1 (Polyquad), Alcon Laboratories, Fort Worth, Texas, USA)[11] or O/CMC (Optive Lubricant Eye Drops preserved with sodium chlorite (Purite) Allergan, Irvine, California, USA)[22] eye-drops for the duration of the study. Assigned treatments were self-administered in both eyes four times a day for 35 days, with the last daily drop administered at bedtime. The second treatment phase was a safety extension; patients administered one drop of assigned treatments in both eyes as needed (ie, *pro re nata* (PRN)) through day 90. Investigators, clinical site staff, the study sponsor, and monitors involved in reporting, obtaining, or reviewing clinical evaluations were masked to treatment assignments. On-treatment follow-up visits were conducted at day 35 (end of treatment phase 1) and day 90 (end of treatment phase 2).

Patients

Eligible patients were aged ≥18 years, were diagnosed with dry eye ≥3 months before screening and were using benzalkonium chloride (BAK)-free eye-drops at least once per day for ≥3 months. At the screening visit, patients were required to have a total ocular surface staining (TOSS) score ≥4 and ≤9 on the 15-point Oxford scale in at least one eye and either unanesthetised Schirmer I test result of 3–9 mm or tear film break-up time ≤30 s (sum of three measurements; mean break-up time per measurement, ≤10 s).

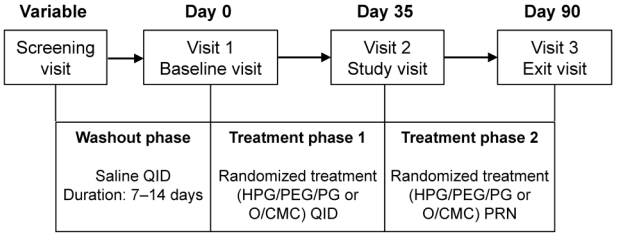

Figure 1 Study design. Visits, phases and treatments are depicted. HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop; O/CMC, osmoprotective carboxymethylcellulose/glycerine eye-drop; PRN, as needed; QID, four times a day.

Key non-inclusion criteria were best corrected visual acuity (BCVA) of 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or worse; established primary or secondary Sjögren syndrome or dry eye symptoms and signs sufficiently severe to indicate high likelihood of Sjögren syndrome; any significant nasolacrimal system disorder; eyelid abnormalities; corneal disorders; use of topical treatments other than BAK-free artificial tears, lubricants or rewetting drops ≤2 weeks before screening; and use of contact lenses ≤2 weeks before screening or during the study.

One eye from each patient was selected as the study eye and used for eye-level efficacy analyses. If both eyes met inclusion criteria, the worse evaluable eye (ie, the eye with the higher TOSS score at baseline) was selected. If TOSS scores were equal between eyes, the right eye was selected as the study eye.

Outcomes and assessments

The primary efficacy end point was TOSS score change from baseline to day 35, and the primary objective was to demonstrate non-inferiority of HPG/PEG/PG compared with O/CMC after 35 days of four times a day administration. Also assessed at day 35 were mean treatment effectiveness and treatment inconvenience scores on the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire. Safety evaluations included extent of treatment exposure, adverse events (AEs), BCVA and ocular signs.

TOSS, BCVA, ocular signs, and AEs were assessed at screening, baseline, day 35 and day 90. IDEEL scores for treatment effectiveness and treatment inconvenience were assessed at day 35 and day 90. The TOSS score was calculated as a composite score of corneal fluorescein staining, nasal conjunctival lissamine green staining and temporal conjunctival lissamine green staining, each scored on a Likert scale (grade 0=absent, 5=severe; maximum total score=15). IDEEL items were scored on a Likert scale from 0=all of the time to 4=none of the time. Treatment effectiveness scores were based on the mean value for IDEEL items 2–5, multiplied by 25. Treatment inconvenience scores were based on the mean value from IDEEL items 6, 8, 9 and 10, multiplied by 25. The possible range of each IDEEL score was 0 (complete disability) to 100 (no disability).

Statistical analyses

Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, North Carolina, USA). Efficacy end points were analysed in the intent-to-treat (ITT) population (all patients who were randomised to treatment). For a given end point, only patients with data for baseline and the appropriate on-treatment visit were included in the analysis. Mean TOSS score change from baseline data were summarised descriptively, and treatment efficacy was inferred from a decrease in TOSS score from baseline to day 35. Comparison of treatment efficacy used two-sided testing based on the least squares (LS) means from an analysis of variance, with a statistical significance level of $p<0.05$. Treatment non-inferiority, based on TOSS score change from baseline to day 35, was to be concluded if the upper limit of the two-sided CI was <2 units. IDEEL scores were summarised descriptively and treatment comparisons were made using two-sided 95% CIs. AEs were coded using the *Medical Dictionary for Regulatory Activities V.16.0*, and AEs, BCVA and ocular signs were summarised descriptively for the safety population (all patients who received at least one dose of study medication).

Based on an assumed SD of 2.5 units for the non-inferiority margin for TOSS scores, a minimum sample size of 40 patients

per group in the ITT data set was determined to provide 94% power to demonstrate non-inferiority of HPG/PEG/PG compared with O/CMC with a non-inferiority margin of 2 units.

RESULTS

Patients

Of the 105 patients enrolled, 94 were randomised to treatment and included in the ITT population (HPG/PEG/PG, n=46; O/CMC, n=48). Of the 11 patients enrolled but not randomised, 9 were screen failures (ie, did not meet eligibility criteria), 1 discontinued because of an AE during the washout/run-in period and 1 was lost to follow-up before randomisation. Mean±SD patient age was 64.4±13.7 years. Most patients were female (n=79/94, 84%) and white (n=87/94, 93%). Baseline TOSS was 5.5±1.8; baseline scores were similar between groups. There were no meaningful between-group differences in patient demographics or baseline characteristics (table 1). The study was completed by 82 patients (HPG/PEG/PG, n=41/46; O/CMC, n=41/48). Reasons for discontinuation were AEs (HPG/PEG/PG, n=3; O/CMC, n=4); patient withdrawal (HPG/PEG/PG, n=0; O/CMC, n=3); and loss to follow-up (HPG/PEG/PG/, n=2; O/CMC, n=0). One patient randomised to O/CMC withdrew before exposure to study treatment and was excluded from the safety population (n=93).

Efficacy

At baseline, TOSS score (LS mean±SE) was 5.5±0.27 points in both treatment groups; TOSS scores at day 35 were 3.5±0.34 points and 3.9±0.35 points in the HPG/PEG/PG and O/CMC groups, respectively, indicating that both treatments reduced ocular surface staining indicative of epithelial damage. TOSS score change from baseline to day 35 was −2.2±0.33 points with HPG/PEG/PG and −1.7±0.34 points with O/CMC (treatment difference, −0.47±0.47 points; 95% CI −1.41 to 0.47 points; p=0.318; figure 2). Because the upper 95% CI was <2 points, the criterion for non-inferiority of HPG/PEG/PG was met.

Table 1 Demographic information and baseline characteristics (intent-to-treat population)

	HPG/PEG/PG (n=46)	O/CMC (n=48)
Age, years		
Mean±SD	63.5±13.1	65.2±14.3
Range	28–92	19–84
Sex, n (%)		
Female	39 (84.8)	40 (83.3)
Male	7 (15.2)	8 (16.7)
Race, n (%)		
White	42 (91.3)	45 (93.8)
Asian	2 (4.3)	1 (2.1)
Multiracial	1 (2.2)	1 (2.1)
Black or African-American	0	1 (2.1)
Other	1 (2.2)	0
Total ocular surface staining score*†		
Mean±SD	5.5±1.9	5.5±1.7
Range	0–9	2–10

*HPG/PEG/PG, n=46; O/CMC, n=47.
†Composite of corneal fluorescein staining and conjunctival (nasal and temporal) lissamine green staining, each scored on a 6-point Likert scale (0=absent, 5=severe). Potential score range, 0–15.
HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop; O/CMC, osmoprotective carboxymethylcellulose/glycerine eye-drop.

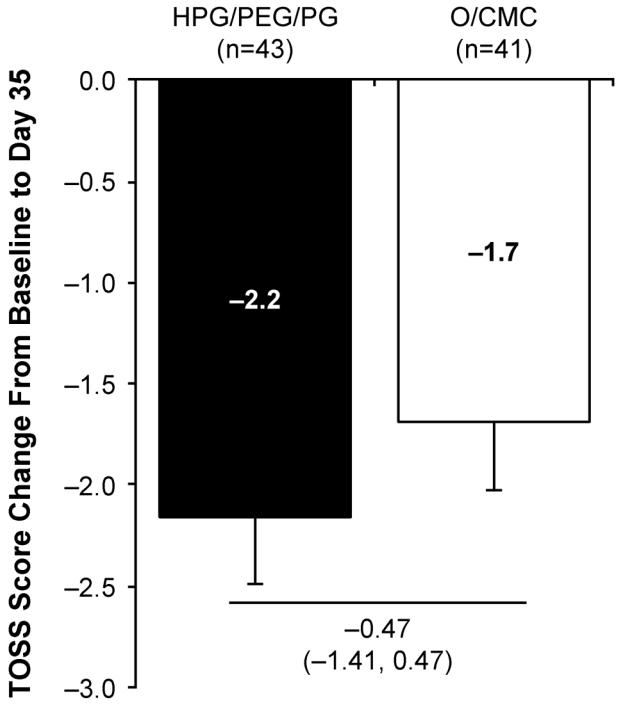

Figure 2 Mean TOSS score change from baseline. Data reflect least squares mean and SE. Mean TOSS scores are indicated within bars; mean treatment group difference (two-sided 95% CI) is indicated below bars; lower scores indicate less ocular surface damage. HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop; O/CMC, osmoprotective carboxymethylcellulose/glycerine eye-drop; TOSS, total ocular surface staining.

IDEEL scores for treatment effectiveness at day 35 were 62.2±4.3 with HPG/PEG/PG and 55.7±4.4 with O/CMC (treatment difference, 6.5±6.2; p=0.294; figure 3). IDEEL scores for treatment inconvenience at day 35 were 69.5±3.0 and 67.1±3.1 with HPG/PEG/PG and O/CMC, respectively (treatment difference, 2.4±4.4; p=0.586; figure 3). Similar efficacy outcomes were observed in both groups at day 90 (PRN

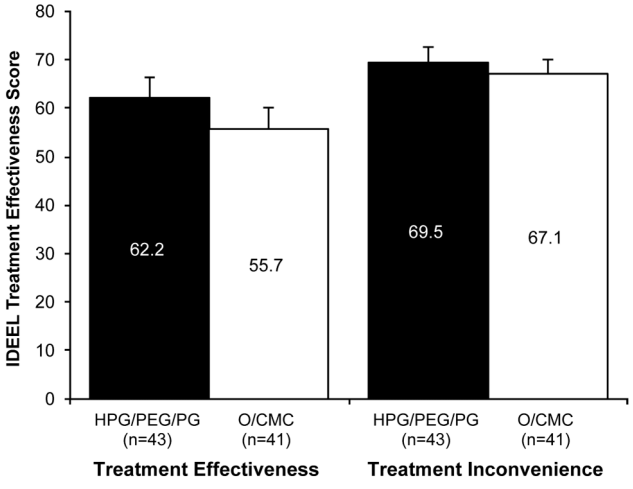

Figure 3 Mean IDEEL score. (A) Treatment effectiveness, (B) treatment inconvenience. Data reflect least squares mean and SE. Mean IDEEL scores are indicated within bars. Potential IDEEL score range, 0–100; higher scores indicate improved impact on everyday life. IDEEL, Impact of Dry Eye on Everyday Life; HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop; O/CMC, osmoprotective carboxymethylcellulose/glycerine eye-drop.

administration) compared with day 35 (four times a day administration). The mean dosing frequency for the day prior to the day 90 visit was 3.9±1.6 with HPG/PEG/PG (median, 4) and 4.5±2.0 with O/CMC (median, 5).

Safety

Exposure duration (mean±SD) during the first treatment phase was 35.5±6.1 days and 32.7±8.6 days with HPG/PEG/PG/ and O/CMC, respectively. Exposure duration during the second treatment phase was 56.2±11.0 days and 55.4±6.5 days with HPG/PEG/PG and O/CMC, respectively. AEs were reported for 14 patients receiving HPG/PEG/PG (35 events) and for 17 patients receiving O/CMC (37 events; table 2). One serious AE (spinal column injury) unrelated to study treatment was reported in the HPG/PEG/PG group. AEs that caused study discontinuation included dry eye, eye irritation, eye pain, eyelid oedema and pruritus. Most treatment-related AEs were local ocular side effects (table 2).

Mean±SD BCVA was similar between groups at baseline (HPG/PEG/PG, 82.5±9.1 letters; O/CMC, 82.2±14.4 letters) and was similar to baseline at day 35 and day 90. The change from baseline was <2 letters in either group. Ocular signs were also generally unchanged from baseline in both groups throughout the study.

DISCUSSION

The standard of care for treating dry eye includes reducing ocular surface damage, alleviating signs and symptoms of dry

Table 2 Adverse events (safety population)

	HPG/PEG/PG (n=46)		O/CMC (n=47)	
Adverse events	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**
Patients with ≥1 AE, n (%)	14 (30.4)	35	17 (36.2)	37
Treatment-related AEs				
Related to treatment	4 (8.7)	6	6 (12.8)	18
Related to administration procedure	0	0	1 (2.1)	2
Non-fatal serious AEs	1 (2.2)	1	0	0
Discontinuations due to AEs	3 (6.5)	5	4 (8.5)	7
Treatment-related AEs	2 (4.3)	3	3 (6.4)	6
AE severity				
Mild	6 (13.0)	17	7 (14.9)	16
Moderate	3 (6.5)	5	4 (8.5)	12
Severe	0	0	1 (2.1)	2
AEs observed in ≥2 events in either group				
Eye irritation	2 (4.3)	3	3 (6.4)	5
Ocular hyperaemia	2 (4.3)	5	0	0
Dry eye	1 (2.2)	2	2 (4.3)	4
Eye pain	1 (2.2)	1	2 (4.3)	4
Blurred vision	1 (2.2)	2	2 (4.3)	4
Eye pruritus	1 (2.2)	2	1 (2.1)	2
Conjunctivitis	1 (2.2)	2	0	0
Eye discharge	1 (2.2)	2	0	0
Rash	1 (2.2)	2	0	0
Sinusitis	0	0	2 (4.3)	2
Foreign body sensation	0	0	1 (2.1)	2
Conjunctival hyperaemia	0	0	1 (2.1)	2
Abnormal sensation in the eye	0	0	1 (2.1)	2
Photophobia	0	0	1 (2.1)	2
Ocular discomfort	0	0	1 (2.1)	2
AEs leading to study discontinuation				
Dry eye	1 (2.2)	2	1 (2.1)	2
Eye irritation	1 (2.2)	1	0	0
Eye pruritus	1 (2.2)	2	0	0
Eye pain	0	0	2 (4.3)	4
Eyelid oedema	0	0	1 (2.1)	1
Treatment-related AEs observed in ≥1 patient in either group				
Eye irritation	2 (4.3)	3	3 (6.4)	5
Dry eye	1 (2.2)	2	2 (4.3)	4
Eye pain	1 (2.2)	1	2 (4.3)	4
Blurred vision	1 (2.2)	2	2 (4.3)	4
Parosmia	1 (2.2)	1	0	0
Abnormal sensation in eye	0	0	1 (2.1)	2
Photophobia	0	0	1 (2.1)	2

AE, adverse event; HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol-based lubricant eye-drop; O/CMC, osmoprotective carboxymethylcellulose/glycerine eye-drop.

eye, and maintaining visual function.[23] Dry eye therapy relies largely on artificial tears that restore the natural tear film and promote tear film stability to protect the ocular surface and improve patients' comfort, vision and quality of life. This study evaluated the effectiveness and safety of two lubricant eye-drops, HPG/PEG/PG and O/CMC, in adults diagnosed with dry eye and experiencing symptoms of dry eye at enrolment. After 35 days of four times a day treatment, TOSS scores, which reflect the degree of corneal and conjunctival damage present, were reduced from baseline in both treatment groups, and non-inferiority of HPG/PEG/PG compared with O/CMC was established. IDEEL scores for treatment effectiveness and treatment inconvenience were comparable between groups at day 35. Similar efficacy results were observed at day 90 with PRN dosing. Most treatment-related AEs were mild ocular side effects, and no new safety concerns were identified for HPG/PEG/PG or O/CMC.

Dry eye often causes desiccation-related and friction-related damage to ocular surface tissues that can be visualised using fluorescein and lissamine green staining of disrupted cell-to-cell junctions and dead or desquamated cells in the cornea and conjunctiva, respectively. Both HPG/PEG/PG and O/CMC hydrate and lubricate the ocular surface. HPG/PEG/PG also increases tear film stability and decreases ocular surface damage by acting as a mucomimetic that binds and protects damaged hydrophobic epithelial tissue to allow the ocular surface to repair itself. O/CMC protects corneal cells from hypertonicity associated with increased osmolarity of the tear film in dry eye and promotes epithelial cell growth.

In this study, patients in both treatment groups had mild to moderate ocular surface staining at baseline. After 35 days of four times a day administration of HPG/PEG/PG or O/CMC, ocular surface staining scores were reduced to a similar extent (2.2 points and 1.7 points, respectively, from 5.5 points at baseline), suggesting that both formulations, which combine several mechanisms of ocular surface repair, were similarly effective in reducing corneal and conjunctival surface damage in patients with dry eye. This finding is consistent with previous studies demonstrating that HPG/PEG/PG and O/CMC decrease corneal and conjunctival staining in patients with dry eye.[16 20 22] HPG/PEG/PG was non-inferior to O/CMC with regard to total ocular staining, and the numerical treatment difference favoured HPG/PEG/PG over O/CMC. Similarly, among 105 patients with dry eye, significantly less corneal and conjunctival stainings were observed in patients receiving HPG/PEG/PG compared with those receiving O/CMC.[16]

Treatment effectiveness was rated with regard to the speed, duration and extent of symptom relief using the IDEEL questionnaire. Scores for IDEEL treatment effectiveness and treatment inconvenience were comparable between groups. Together, the observed improvements in ocular staining and IDEEL scores suggest that HPG/PEG/PG provided patient satisfaction and convenience comparable with O/CMC.

The results of this study demonstrated that the efficacy of HPG/PEG/PG in reducing corneal and conjunctival damage was non-inferior to O/CMC and that patient-reported treatment effectiveness and convenience were comparable between treatments with four times a day and PRN dosing. Corneal and conjunctival staining scores were improved from baseline by 2.2 points with HPG/PEG/PG compared with 1.7 points with O/CMC; additional study is needed to establish whether this difference is clinically significant. Further, patients receiving HPG/PEG/PG reported using numerically fewer daily doses during the PRN phase of the study (3.9 doses with HPG/PEG/PG vs 4.5 doses with O/CMC). This finding suggests that individuals may require less frequent administration of HPG/PEG/PG than of O/CMC to manage their dry eye in a real world setting. The preservatives in these formulations (polyquaternium-1 (HPG/PEG/PG) and sodium chlorite (O/CMC)) are both considered to be less harmful than older preservatives such as BAK.[24] Studies comparing the tolerability of polyquaternium-1 and sodium chlorite are lacking; however, the less frequent dosing of HPG/PEG/PG may result in less cumulative exposure to preservatives with long-term use.

The combined assessment of objective dry eye signs and patient-reported outcomes, and the inclusion of a PRN treatment administration phase were strengths of the study. Limitations included the absence of a treatment cross-over phase and the lack of patient masking because of the inherent differences in the appearance of the product. However, this study was investigator-masked and therefore protected from observer bias.

In summary, HPG/PEG/PG was non-inferior to O/CMC; both study treatments decreased ocular surface staining, indicating improved ocular surface health. HPG/PEG/PG and O/CMC alleviated objective signs and patient-reported symptoms of dry eye and were scored similarly for treatment effectiveness and treatment convenience. Improvement of dry eye signs and symptoms was demonstrated with both, four times a day and PRN dosing, suggesting that both treatments were convenient and effective.

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Contributors All authors were involved in the design and critical revisions of the manuscript and maintained complete control over the direction and content of the paper.

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Patient consent Obtained.

Ethics approval The study protocol was approved by the appropriate institutional review boards. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

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REFERENCES

1 The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5:75–92.
2 Baudouin C, Aragona P, Messmer EM, *et al*. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. *Ocul Surf* 2013;11:246–58.
3 The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5:93–107.
4 Sullivan BD, Crews LA, Messmer EM, *et al*. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol* 2014;92:161–6.
5 Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea* 2004;23:762–70.

6 Williamson JF, Huynh K, Weaver MA, *et al*. Perceptions of dry eye disease management in current clinical practice. *Eye Contact Lens* 2014;40:111–15.
7 Friedman NJ. Impact of dry eye disease and treatment on quality of life. *Curr Opin Ophthalmol* 2010;21:310–16.
8 Paulsen AJ, Cruickshanks KJ, Fischer ME, *et al*. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol* 2014;157:799–806.
9 Miljanović B, Dana R, Sullivan DA, *et al*. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol* 2007;143:409–15.
10 Labetoulle M, Baudouin C. From pathogenic considerations to a simplified decision-making schema in dry eye disease. *J Fr Ophtalmol* 2013;36:543–7.
11 Benelli U. Systane lubricant eye drops in the management of ocular dryness. *Clin Ophthalmol* 2011;5:783–90.
12 Aguilar AJ, Marquez MI, Albera PA, *et al*. Effects of Systane® Balance on noninvasive tear film break-up time in patients with lipid-deficient dry eye. *Clin Ophthalmol* 2014;8:2365–72.
13 McDonald M, Schachet JL, Lievens CW, *et al*. Systane® ultra lubricant eye drops for treatment of contact lens-related dryness. *Eye Contact Lens* 2014;40:106–10.
14 Hartstein I, Khwarg S, Przydryga J. An open-label evaluation of HP-Guar gellable lubricant eye drops for the improvement of dry eye signs and symptoms in a moderate dry eye adult population. *Curr Med Res Opin* 2005;21:255–60.
15 Springs CL. Novel hydroxypropyl-guar gellable lubricant eye drops for treatment of dry eye. *Adv Ther* 2010;27:681–90.
16 Davitt WF, Bloomenstein M, Christensen M, *et al*. Efficacy in patients with dry eye after treatment with a new lubricant eye drop formulation. *J Ocul Pharmacol Ther* 2010;26:347–53.
17 Rangarajan R, Kraybill B, Ogundele A, *et al*. Effects of a hyaluronic acid/hydroxypropyl guar artificial tear solution on protection, recovery, and lubricity in models of corneal epithelium. *J Ocul Pharmacol Ther* 2015;31:491–7.
18 Torkildsen G. The effects of lubricant eye drops on visual function as measured by the Inter-blink interval Visual Acuity Decay test. *Clin Ophthalmol* 2009;3:501–6.
19 Garrett Q, Simmons PA, Xu S, *et al*. Carboxymethylcellulose binds to human corneal epithelial cells and is a modulator of corneal epithelial wound healing. *Invest Ophthalmol Vis Sci* 2007;48:1559–67.
20 Guillon M, Maissa C, Ho S. Evaluation of the effects on conjunctival tissues of Optive eyedrops over one month usage. *Contact Lens Anterior Eye* 2010;33:93–9.
21 Kaercher T, Buchholz P, Kimmich F. Treatment of patients with keratoconjunctivitis sicca with Optive: results of a multicenter, open-label observational study in Germany. *Clin Ophthalmol* 2009;3:33–9.
22 Baudouin C, Cochener B, Pisella PJ, *et al*. Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease. *Eur J Ophthalmol* 2012;22:751–61.
23 American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Dry Eye Syndrome. 2013. http://www.aao.org/ppp
24 Tong L, Petznick A, Lee S, *et al*. Choice of artificial tear formulation for patients with dry eye: where do we start? *Cornea* 2012;31(Suppl 1):S32–6.