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Evaluation of an enhanced viscosity artificial tear for moderate to severe dry eye disease: A multicenter, double-masked, randomized 30-day study

Christopher Lievens[a], Gregg Berdy[b], David Douglass[c], Stephen Montaquila[d], Hugh Lin[e,1], Peter Simmons[e,2], Cindy Carlisle-Wilcox[e], Joseph Vehige[e], Sameena Haque[f,*]

[a] Southern College of Optometry, Memphis, TN, USA
[b] Washington University School of Medicine, and Ophthalmology Associates, Saint Louis, MO, USA
[c] Eye Center Northeast, Bangor, ME, USA
[d] West Bay Eye Associates, Warwick, RI, USA
[e] Allergan Clinical Research, Irvine, CA, USA
[f] Allergan International Medical Affairs, Marlow, Buckinghamshire, UK

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ABSTRACT

Purpose: In a randomized, controlled clinical trial, two lubricant artificial tear formulations with enhanced viscosity were compared: an investigational product at the time, containing carboxymethylcellulose 1.0% and glycerin 0.9% (CMC-GLY) with osmoprotectants, and a standard formula containing carboxymethylcellulose 1.0% alone (CMC).

Methods: This double-masked study recruited patients with moderate to severe dry eye at 10 US centers. After a 7-day run-in with CMC 0.5% (Refresh Tears) patients were randomized to use either CMC-GLY or CMC as needed, but at least 2 times daily for 30 days. Patients were stratified by Ocular Surface Disease Index© (OSDI) score into moderate (23–32) and severe (> 32–65) subgroups. Assessments included OSDI (primary efficacy variable), corneal and conjunctival staining, tear break-up time (TBUT), symptom surveys, and safety variables. Study visits were days 1 (baseline/randomization), 7, and 30.

Results: A total of 188 patients (94 CMC-GLY, 94 CMC) were enrolled. The severe subgroup had 67 CMC-GLY and 65 CMC patients. OSDI scores progressively improved and were similar at day 30 between treatment groups. At day 7, only the CMC-GLY group demonstrated significant improvements from baseline in OSDI score (all patients $p < 0.001$, severe $p < 0.001$), corneal staining ($p = 0.004$), and TBUT ($p < 0.001$). Between-group dose frequency for CMC-GLY was lower at day 7 ($p = 0.031$). Other efficacy results were similar between groups. The most commonly reported adverse event in both groups was blurred vision.

Conclusions: Overall, the CMC-GLY artificial tear formulation was as effective as the CMC formulation. CMC-GLY demonstrated improvements at an earlier stage (day 7). Both artificial tear formulations were safe and well tolerated, with no treatment-related serious adverse events. These results support the use of the CMC-GLY artificial tear formulation as an effective treatment to reduce the symptoms and signs of dry eye disease.

1. Introduction

Dry eye disease is a multifactorial disease of the ocular surface that is estimated to cause symptoms in 5%–50% of the global population [1,2]. Dry eye symptoms impact daily functions including reading, driving, professional work, and social activities, significantly diminishing quality of life [3,4]. Artificial tears (lubricant eye drops or gels) are often used as primary therapy for mild to moderate disease and in combination with pharmacological agents or surgical procedures in more severe disease [5,6]. With better understanding of the roles of tears, tear film osmolarity, and ocular surface inflammation in dry eye disease [7–9], development of novel artificial lubricants has focused on

* Corresponding author at: Allergan International Medical Affairs, The Parkway, Marlow, Buckinghamshire, SL7 1YL, UK.
E-mail addresses: clievens@sco.edu (C. Lievens), gregg.berdy@youreyedoc.com (G. Berdy), drd@eyecenternortheast.com (D. Douglass), drmontaquila@westbayeye.com (S. Montaquila), hughlin@gmail.com (H. Lin), pasimmons17@gmail.com (P. Simmons), Carlisle_Cindy@allergan.com (C. Carlisle-Wilcox), j.vehige@sbcglobal.net (J. Vehige), Haque_Sameena@allergan.com (S. Haque).
[1] Present address: Genentech, South San Francisco, CA, USA.
[2] Present address: PCS research, Yorba Linda, CA, USA.

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interaction with ocular surface cells, enhancing protection by preventing cell volume loss, cellular stress, and inflammatory reactions, as well as eliminating damaging preservatives. For many patients with dry eye, artificial tears with higher viscosity, or gel-type tears, are preferred for their extended efficacy due to enhanced ocular residence [10,11]. In addition, these mid-viscosity gel-type tears are more suitable for nighttime than conventional tears, yet are easier to apply for many users than gel and ointment products in tubes. Overall, the more viscous gel-type artificial tears are associated with greater improvements in signs and symptoms of dry eye compared with standard low-viscosity lubricating eye drops [12–14]. If viscosity is too high, it may reduce tolerability due to blur, stickiness, and build-up of residue on the lids and lashes; however, it is also essential that sufficient viscosity is retained under shear stress (during blinking) in order to maintain ocular residence [15].

Carboxymethylcellulose sodium (CMC) is a well-established polymer used in lubricating drops that has been shown to bind to the corneal surface, increasing retention time and promoting corneal wound healing [11,16–19]. CMC (1.0%) is the active ingredient in Refresh Liquigel® Lubricant Eye Gel (Allergan plc, Dublin, Ireland), and is approved for the temporary relief of burning, irritation, and discomfort due to dryness of the eye. Increasing the concentration of CMC (e.g., from 0.5% to 1.0%) and/or the use of higher–molecular-weight polymers enhances viscosity and ocular residence time [14]. A new formulation (Refresh Optive® Gel Drops Lubricant Eye Gel, Allergan plc, Dublin, Ireland) consists of a combination of CMC (1.0%) and glycerin (0.9%) (CMC-GLY). The novel CMC-GLY formulation contains glycerin as a second active ingredient, a small molecule that rapidly enters ocular surface cells and assists in the maintenance of cell hydration and normal osmotic balance [20]. CMC-GLY also contains L-carnitine and erythritol as compatible solutes (osmoprotectants) providing osmotic balance, and the preservative Purite®. These intracellular osmolytes displace excessive salt [21,22], help maintain cell volume [21,22], and protect against the pro-inflammatory hyperosmotic stress that is characteristic of dry eye [20,23].

The objective of this study was to evaluate the efficacy, safety, and patient acceptability of this new lubricant eye gel containing CMC 1.0% and glycerin 0.9% in subjects with signs and symptoms of dry eye disease, compared with the standard formula containing CMC 1.0% alone (Refresh Liquigel).

2. Methods

2.1. Study design

This double-masked, randomized, 2-arm, parallel-group study was conducted at 10 clinical sites in the United States between November 2014 and March 2015 (ClinicalTrial.gov identifier: NCT02280473). The study was carried out in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice. Investigators at each site obtained study approval from their institutional review board or an independent ethics committee, and all subjects provided written informed consent prior to the start of any study procedures.

2.2. Inclusion and exclusion criteria

Healthy male or female subjects ≥18 years of age were enrolled if they had moderate to severe symptoms according to an Ocular Surface Disease Index© (OSDI) score ≥28 and ≤65 (based upon a 0–100 scale) at screening and OSDI score ≥23 and ≤65 at the baseline visit. Subjects were required to have used artificial tears at least twice daily on average for at least 1 month prior to screening. Subjects had to have grade ≥1 staining (modified National Eye Institute Grid score: range 0–5) in ≥1 area of the cornea (5 areas examined) or conjunctiva (6 areas examined) in at least 1 eye at screening and day 1. At screening, subjects were also required to have 3 consecutive tear break-up time (TBUT) tests ≤ 10 s in at least 1 eye, a distance visual acuity ≥ 20/32 Snellen equivalent in each eye (3-meter LogMAR chart with existing correction), and intraocular pressure (IOP) ≤21 mm Hg in both eyes. Subjects who discontinued use of pre-study artificial tears at screening, received monotherapy for glaucoma or ocular hypertension, or had used cyclosporine ophthalmic emulsion (Restasis®, Allergan plc, Dublin, Ireland) for at least 3 months prior to screening with no anticipated dosage adjustments were eligible for the study.

Key exclusion criteria included Schirmer test (with anesthesia) ≤2 mm/5 min in either eye at screening, corneal or conjunctival staining score of 5 at screening or day 1 in any area of either eye, and cumulative corneal staining score of > 18 in all 5 zones at screening or day 1 in either eye. Subjects using systemic medications < 3 months prior to screening that may have affected a dry eye condition or vision, with a history of prior ocular/ophthalmic surgery or trauma within 6 months prior to screening that could have affected corneal sensitivity and/or tear distribution, or currently using or having used topical ocular medication within 2 weeks of screening were excluded. Subjects being treated with both IOP-lowering medication and cyclosporine ophthalmic emulsion were not considered for enrollment.

2.3. Study treatment

The study consisted of a baseline visit (day 1) and 2 follow-up visits at days 7 (± 3 days) and 30 (± 7 days; or early exit). At the screening visit, all subjects who met inclusion/exclusion criteria received CMC 0.5% (Refresh Tears®; Allergan plc, Dublin, Ireland), and were asked to instill 1–2 drops at least twice daily in each eye for 7 days (run-in period) prior to the baseline visit. Following the run-in period, subjects who still met study criteria were randomized 1:1 on day 1 to treatment with CMC-GLY or CMC (1.0%) alone. Subjects were also stratified at baseline according to their OSDI score into moderate (23–32) and severe (> 32–65) subgroups. An automated Interactive Voice Response System or Interactive Web Response System Randomization was used to manage randomization and treatment assignment based on a scheme prepared by Allergan Biostatistics. Subjects were instructed to instill 1–2 drops of their assigned study product in each eye, as needed, but at least twice daily for 30 days. Study products, as well as the run-in product, were provided in identical 15-mL bottles to maintain subject and investigator masking. Monitoring of treatment compliance was achieved using the Study Product Usage Questionnaire at all follow up visits; investigators also recorded the number of units dispensed and unused units returned throughout the study.

2.4. Outcome measures

The change in OSDI score from baseline at day 30 was the primary efficacy variable. The OSDI is scored on a scale of 0 to 100 [24], with higher scores representing more severe disease and a negative change from baseline demonstrating improvement. The change from baseline in OSDI score at day 7 was a secondary efficacy variable. Additional secondary efficacy measures included TBUT measured 3 times in each eye during the 2-min period following instillation of sodium fluorescein onto the superior bulbar conjunctiva. In each eye, corneal staining evaluated in 5 zones with fluorescein and interpalpebral conjunctival staining evaluated in 6 zones with lissamine green were assessed using the modified NEI Grid graded on a scale of 0 (no staining) to 5 (> 30 dots plus confluence) [25]. Schirmer tests (with anesthesia) were performed in each eye after completing all other assessments, initiated 4 min after instillation of a drop of anesthesia and the amount of wetting of test strips measured 5 min later.

Other efficacy assessments included 2 subject surveys: 1 concerning current symptoms of burning/stinging, grittiness/foreign sensation, dryness, difficult/uncomfortable vision, and overall pain/discomfort, and the other consisting of 10 questions about the short- and long-term experience, primarily in comfort and vision, with the test products.

Grading ranged from 0 (none) to 100 (maximum) on a visual analog scale. Subjects also reported their daily dosing frequency on average over the past week and the timing of the last dose.

Safety assessments were performed in both eyes and included monitoring adverse events (coded using the *Medical Dictionary for Regulatory Activities*, version 18.0), biomicroscopy examinations performed in each eye (without pupil dilation), currently corrected distance visual acuity and best-corrected distance visual acuity measured in each eye, and IOP (with anesthesia and fluorescein) assessed in each eye at approximately the same time at each visit using the Goldmann applanation tonometer.

3. Statistical analysis

The intent-to-treat (ITT) population consisting of all randomized subjects was used for efficacy analysis based on the randomized treatment. The per protocol population, consisting of randomized subjects with no significant protocol violations prior to database lock, was used for sensitivity efficacy analysis. The safety population, consisting of all subjects receiving at least one treatment dose, was used for safety analysis based on the actual treatment received.

The primary efficacy analysis of the change from baseline in OSDI score at day 30 was performed using an analysis of variance (ANOVA) model, with treatment and stratification factors based on baseline OSDI score (moderate or severe) as fixed effects. Analysis was performed on the ITT population using the last observation carried forward method following a strategy of combined noninferiority and superiority tests [26]. Noninferiority was tested using the confidence interval (CI) procedure, and if the upper limit of the 2-sided 95% CI based on treatment difference (CMC-GLY minus CMC) was less than 7.3 units [27], then the CMC-GLY formulation was considered noninferior to CMC. The change from baseline in the OSDI score at day 7 was analyzed using the same model described above for the primary efficacy variable. Descriptive statistics of change from baseline in the OSDI score for each visit were tabulated and within-group changes from baseline were analyzed using the paired *t* test at each visit. Subgroup analysis of baseline and change from baseline in OSDI scores, based on baseline OSDI score stratum (moderate vs severe), was performed in the ITT population using a 1-way ANOVA model with treatment as the fixed effect.

For other efficacy measures including TBUT, corneal and conjunctival staining, and Schirmer test, the worse eye at baseline was used for analysis. Continuous variables were summarized using descriptive statistics, and analyzed using ANOVA models or Wilcoxon Rank Sum test for between-group differences and paired *t* tests for within-group differences. Categorical variables were summarized by frequency and percentage, and were analyzed using Pearson's chi-square test or Fisher's exact-test. For safety, the number and percentage of all adverse events reported were tabulated for each treatment group. Biomicroscopy findings, currently corrected distance visual acuity, best-corrected distance visual acuity, and IOP measures were summarized with descriptive statistics and the frequency distributions analyzed using Pearson's chi-square test or Fisher's exact-test, where appropriate.

To obtain 85% power for a 1-sided noninferiority test for a between-group difference of 7.3 units in mean change from baseline in total OSDI score at day 30, 85 subjects per treatment group were required based on a 1-sided type I error rate of 0.025 and the assumptions of no inherent treatment difference and a common standard deviation (SD) of 15.7. With a 1:1 treatment allocation and combined dropout and protocol deviation rate of 5%, a total of 180 subjects were required to be enrolled to have 170 subjects complete the study through day 30. Sample size and power calculations were performed using procedure MTE0-1 of the nQuery Advisor software, version 6.01 (Statistical Solutions, Boston, MA, US).

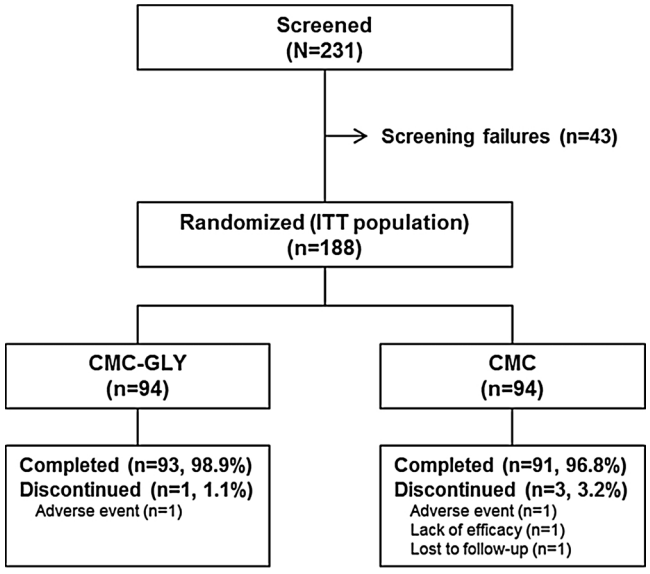

Fig. 1. Subject flow diagram. CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%, ITT = intent-to-treat.

4. Results

4.1. Subject disposition and baseline characteristics

A total of 188 subjects were enrolled and received CMC 0.5% alone during a 7-day masked run-in period, after which they were randomized to receive treatment with CMC-GLY (94 subjects; 67 with severe disease) or CMC 1.0% alone (94 subjects; 65 with severe disease). Of the randomized subjects, 184 (97.9%) went on to complete the study. Four (2.1%) subjects discontinued during the course of the study: due to adverse events (n = 2 [1.1%]), lack of efficacy (n = 1 [0.5%]) and loss to follow-up (n = 1 [0.5%]) (Fig. 1). There were no significant differences in subject characteristics and baseline clinical assessments between the treatment groups (Table 1). Mean (SD) age of subjects was 51.2 (15.4) years, and most (n = 139 [73.9%]) were over 40 years of

Table 1
Demographics and baseline characteristics.

Characteristic	CMC-GLY (n = 94)	CMC (n = 94)	P value[a]
Mean (SD) age, years	51.7 (14.8)	50.7 (15.9)	0.633
> 40, n (%)	72 (76.6)	67 (71.3)	
Sex, n (%)			0.574
Female	78 (83.0)	75 (79.8)	
Male	16 (17.0)	19 (20.2)	
Race, n (%)			0.817
Caucasian	83 (88.3)	84 (89.4)	
Non-Caucasian	11 (11.7)	10 (10.6)	
Mean OSDI score (SD)	42.4 (11.7)	40.4 (11.2)	0.230[b]
Moderate disease (OSDI 23–32)	28.6 (2.5)	28.6 (2.6)	
Severe disease (OSDI > 32)	48.0 (9.0)	45.7 (9.4)	
Mean TBUT (SD), sec	5.4 (1.7)	5.4 (2.1)	0.968[b]
Mean Schirmer's test (SD), mm/5 min	10.0 (7.2)	11.3 (8.5)	0.244[b]
Mean staining score (SD)			
Combined corneal/conjunctival	10.9 (7.2)	11.8 (7.2)	0.261[c]
Corneal	4.9 (3.7)	5.0 (3.6)	0.683[c]
Conjunctival	6.2 (4.8)	7.1 (4.8)	0.196[c]

CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%, OSDI = Ocular Surface Disease Index©, SD = standard deviation, TBUT = tear break-up time.
[a] 2-sample *t* test for continuous variables; Pearson's chi-square test for categorical variables.
[b] Analysis of variance model with treatment as the fixed effect.
[c] Wilcoxon Rank Sum test.

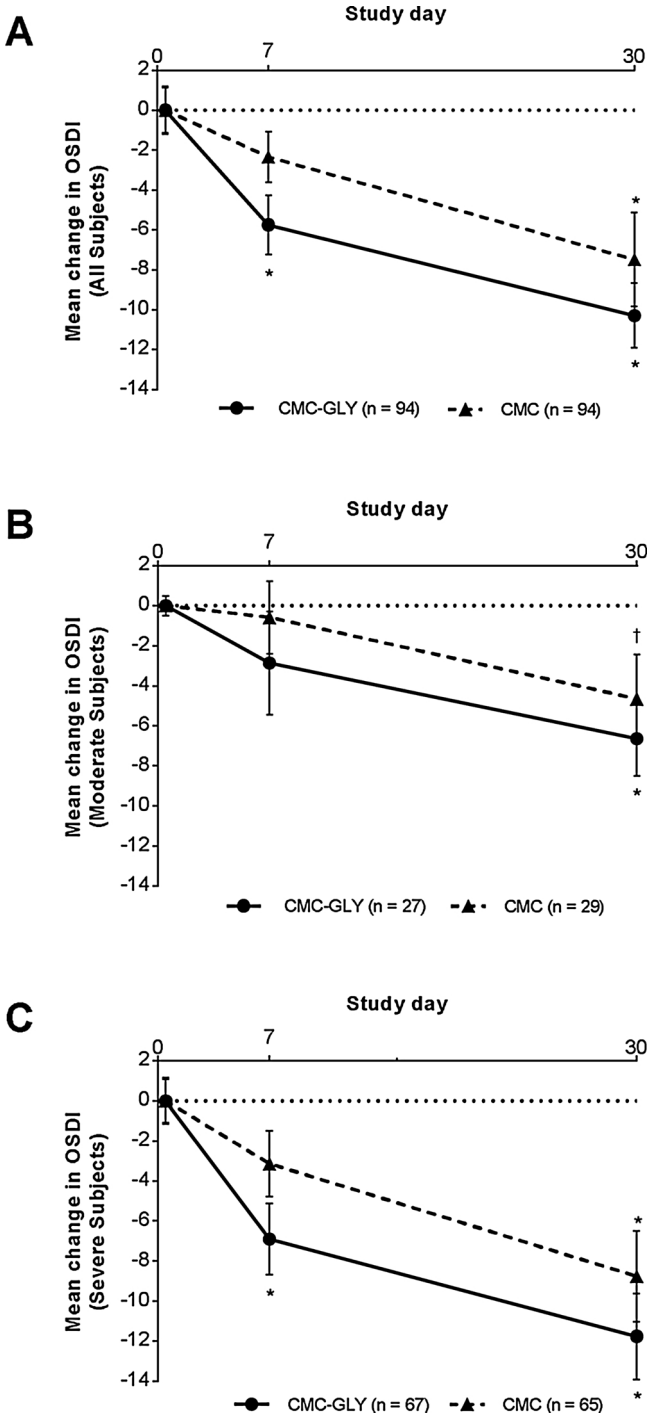

Fig. 2. Change in Ocular Surface Disease Index© (OSDI) score from baseline in (A) all subjects (n = 188), (B) subjects (n = 56) with moderate dry eye (OSDI score 23 to 32) and (C) subjects (n = 132) with severe dry eye (OSDI score > 32) at baseline. Data points represent mean ± standard error mean in the intent-to-treat population; *$p \leq 0.001$; †$p = 0.046$ by paired *t* test. CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%. P values represent within-group change from baseline.

age. The majority of subjects were female (n = 153 [81.4%]) and Caucasian (n = 167 [88.8%]). Based on the reduced TBUT (5.4 s) and normal Schirmer scores (≥10 mm/5 min) at baseline, the majority of subjects had evaporative dry eye.

4.2. Efficacy outcomes

Significant improvements in OSDI score from baseline were observed with CMC-GLY at both days 7 and 30 ($p < 0.001$), and with CMC at day 30 ($p < 0.001$) (Fig. 2 and Table 2). At day 30, the mean (SD) change in OSDI score from baseline was −10.3 (15.9) for CMC-GLY and −7.5 (16.6) for CMC. In the primary efficacy analysis, the criterion for noninferiority of CMC-GLY compared with CMC was met: the least squares mean difference between the treatment groups was −2.7 with a 95% CI of (−7.4, 1.9); the upper limit of the 95% CI was below the prespecified clinical margin of 7.3. Superiority testing indicated that between-group differences in the mean change from baseline in OSDI score were not significantly different at any follow-up visit.

In the subgroup analysis, significant improvements in OSDI score from baseline were observed following treatment with CMC-GLY in the moderate disease (OSDI score: 23–32) subgroup at day 30 ($p = 0.001$) and in the severe disease (OSDI score: > 32) subgroup at days 7 and 30 ($p < 0.001$). Treatment with CMC also resulted in significant improvements in OSDI score from baseline in the moderate ($p < 0.05$) and severe ($p < 0.001$) subgroups at day 30 (Fig. 2).There were no significant differences between CMC-GLY and CMC in the mean change from baseline in OSDI scores at days 7 and 30, among subjects who had moderate or severe OSDI scores at baseline.

Significant improvements from baseline in TBUT were observed following treatment with CMC-GLY at days 7 ($p < 0.001$) and 30 ($p = 0.002$) and with CMC at day 30 ($p < 0.001$) (Fig. 3 and Table 2). Combined corneal/conjunctival staining significantly improved from baseline in both the CMC-GLY and CMC groups at days 7 and 30 ($p \leq 0.02$) (Fig. 4). Corneal staining was significantly improved from baseline in only the CMC-GLY group at days 7 and 30 ($p \leq 0.017$; Fig. 4 and Table 2), while conjunctival staining was significantly improved in both the CMC-GLY and CMC groups at days 7 and 30 ($p \leq 0.019$) (Fig. 4). No statistically significant differences were observed between treatment groups in the mean change from baseline in TBUT, combined corneal/conjunctival staining, corneal staining, and conjunctival staining. There were no statistically significant differences within or between the CMC-GLY and CMC groups for the mean change from baseline in Schirmer test score at each follow-up visit. At day 30, the mean (SD) change from baseline in Schirmer test score was 0.8 (5.5) mm/5 min for CMC-GLY and 0.5 (6.6) mm/5 min for CMC.

Results of the current symptom and eye drop experience surveys were generally comparable between the treatment groups. Both treatment groups demonstrated significant improvements in eye dryness score from baseline with a mean (SD) change of −8.1 (24.6) for CMC-GLY ($p = 0.002$) and −16.2 (28.7) for CMC ($p < 0.001$). A significant between-group difference was observed in the change from baseline in dryness score in favor of CMC at day 30 ($p = 0.037$). No significant differences between the CMC-GLY and CMC groups were observed for mean change in burning/stinging, grittiness/foreign body sensation, difficult/uncomfortable vision, and overall ocular pain/discomfort scores. At day 30, there were no significant between-group differences for the following 8 (of the 10) eye drop experience questions: first application experience of the eye drop in terms of “no burning or stinging”, “no blurring or interference with vision”, “feels substantial and optimally thick”; within 5 min after application, “relief of dry eye discomfort”; and within the past few days, “did not cause eyes/eyelashes to become matted/crusty”, “vision is clear and comfortable”, “long lasting relief of dry eye discomfort”, and “overall liked these eye drops”. For questions regarding eye comfort at first application of study product (69.1 [30.0] vs 59.3 [32.8]; $p = 0.041$) and vision interference within 10 min of application of study product (70.7 [31.8] vs 57.3 [36.5]; $p = 0.009$), CMC elicited a more favorable mean (SD) response compared with CMC-GLY. Usage of CMC-GLY was lower than that of CMC at day 7 (mean [SD]: 2.7 [1.0] vs 3.2 [1.7] drops/day, $p = 0.031$) and similar at day 30 (mean [SD]: 2.7 [0.9] vs 3.0 [1.2] drops/day,

Table 2
Change from baseline and between group comparison at day 7 and day 30 in OSDI score, corneal staining, TBUT, and dose frequency.

Efficacy measure	Treatment	Day 7		Day 30	
		Change from baseline comparison	Between group comparison	Change from baseline comparison	Between group comparison
OSDI	CMC-GLY	$p < 0.001$	NS	$p < 0.001$	NS
	CMC	NS		$p < 0.001$	
TBUT	CMC-GLY	$p < 0.001$	NS	$p = 0.002$	NS
	CMC	NS		$p < 0.001$	
Corneal staining	CMC-GLY	$p = 0.004$	NS	$p = 0.017$	NS
	CMC	NS		NS	
Dose frequency	CMC-GLY	$p = 0.025$ (2.7 drops/day[a])	$p = 0.031$	$p = 0.008$ (2.7 drops/day[a])	NS
	CMC	NS (3.2 drops/day[a])		$p = 0.476$ (3.0 drops/day[a])	

CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%, NS = non-significant.
[a] Mean patient reported drop use.

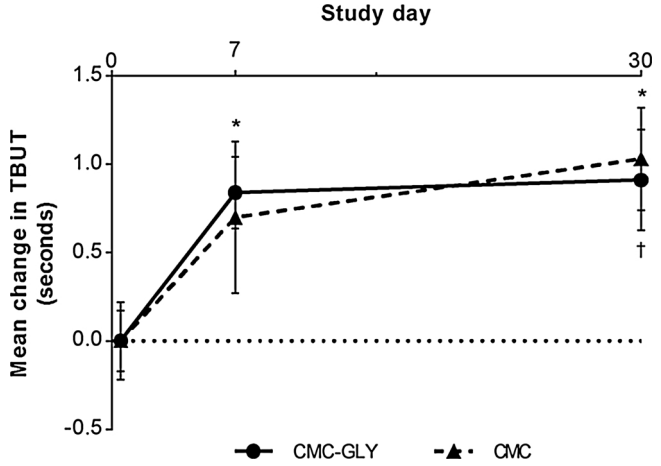

Fig. 3. Change from baseline in tear break-up time (TBUT). Data points represent mean ± standard error mean in the intent-to-treat population; *$p < 0.001$; †$p = 0.002$ by paired *t* test. CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%. CMC-GLY (n = 94, 94, 93) and CMC (n = 94, 93, 91) at baseline, day 7 and 30, respectively. P values represent within-group change from baseline.

$p = 0.073$). Furthermore, usage of CMC-GLY at both days 7 (2.7 [0.96] drops/day) and 30 (2.7 [0.90] drops/day) was statistically significantly less ($p = 0.025$ at day 7 and $p = 0.008$ at day 30) versus baseline run-in product usage (3.0 [1.24] drops/day) (Table 2).

4.3. Safety

Adverse events of any causality were reported for 14 (14.9%) subjects in both CMC-GLY and CMC groups (Table 3). Treatment-related adverse events occurred in 8 (8.5%) subjects in the CMC-GLY and 7 (7.4%) subjects in the CMC group; blurred vision was the most common treatment-related adverse event (7 [7.4%] subjects receiving CMC-GLY; 5 [5.3%] subjects receiving CMC). Two subjects discontinued the study due to treatment-emergent adverse events: 1 subject in the CMC-GLY group experienced blurred vision and conjunctival hyperemia and 1 subject in the CMC group had corneal abrasion (not considered treatment-related by the investigator). One subject in the CMC group experienced a serious adverse event of hyphema that was not considered treatment-related by the investigator and resolved on the same day it occurred. No deaths were reported in the study.

Clinically significant biomicroscopy findings (defined as more than 1 severity grade increase [worsening] from baseline) in either eye at 1 or more visits were reported in 9 (9.6%) subjects in the CMC-GLY group and 13 (13.8%) subjects in the CMC group. The most common biomicroscopy findings were hyperemia (4 [4.3%] with CMC-GLY and 5 [5.3%] with CMC) and edema (3 [3.2%] with CMC-GLY and 2 [2.1%] with CMC). There were no significant differences between the 2 treatment groups in the frequency distribution of change from baseline in currently corrected distance visual acuity or best-corrected distance visual acuity at days 7 or 30. Intraocular pressure in the eye with the worse change from baseline at each visit was similar between treatment groups; mean change (IOP increase) from baseline at days 7 and 30 was ≤ 0.6 mm Hg with both CMC-GLY and CMC.

5. Discussion

Artificial tears (lubricant drops and gels) are often employed as the primary treatment option for dry eye, to supplement the deficient tear film critical for ocular comfort and adequate vision. There are a number of gel-based artificial tear formulations, each with different physicochemical properties (e.g., viscoelasticity) due to the presence of various polymers or osmoprotectants. The concentration, types of polymers, osmotic balance, use of osmoprotectants, type of preservative, buffer, and combination of these ingredients may distinguish one formulation from another with respect to improvements in signs and symptoms, as well as tolerability.

In this study, a novel CMC-GLY lubricant eye gel formulation was found to be noninferior to the standard formula containing CMC alone in terms of dry eye symptom relief. Both formulations were associated with significant improvements in signs and symptoms of dry eye after 30 days. Symptoms were significantly improved with CMC-GLY and CMC at day 30 in the overall population and in subgroups stratified by dry eye severity, and with CMC-GLY at day 7 in the overall population and the severe dry eye subgroup. Based on reported minimal clinically important difference thresholds for the OSDI in patients with mild-moderate dry eye (4.5–7.3) and severe dry eye (7.3–13.4) [27], and the magnitude of OSDI change in the overall population and dry eye subgroups in this study, both formulations appear to provide clinically relevant improvements in dry eye symptoms.

No between-group differences were observed in any other outcome measures. TBUT significantly improved from baseline in both CMC-GLY and CMC groups at day 30, and in the CMC-GLY group at day 7. In each case, the change in TBUT was below the 5 s threshold considered a clinically important difference in the recent dry eye guidelines [28]. CMC-GLY and CMC demonstrated significant improvements from baseline in combined (corneal and conjunctival) and conjunctival staining at day 30 and at day 7, and the CMC-GLY group had significant improvement in corneal staining at both day 30 and day 7. Ocular symptoms also improved from baseline in both groups, but there were no significant changes in Schirmer test score. A significant difference was observed in 2 of 10 questions regarding experience with study product at day 30 and reported product use at day 7, in favor of CMC.

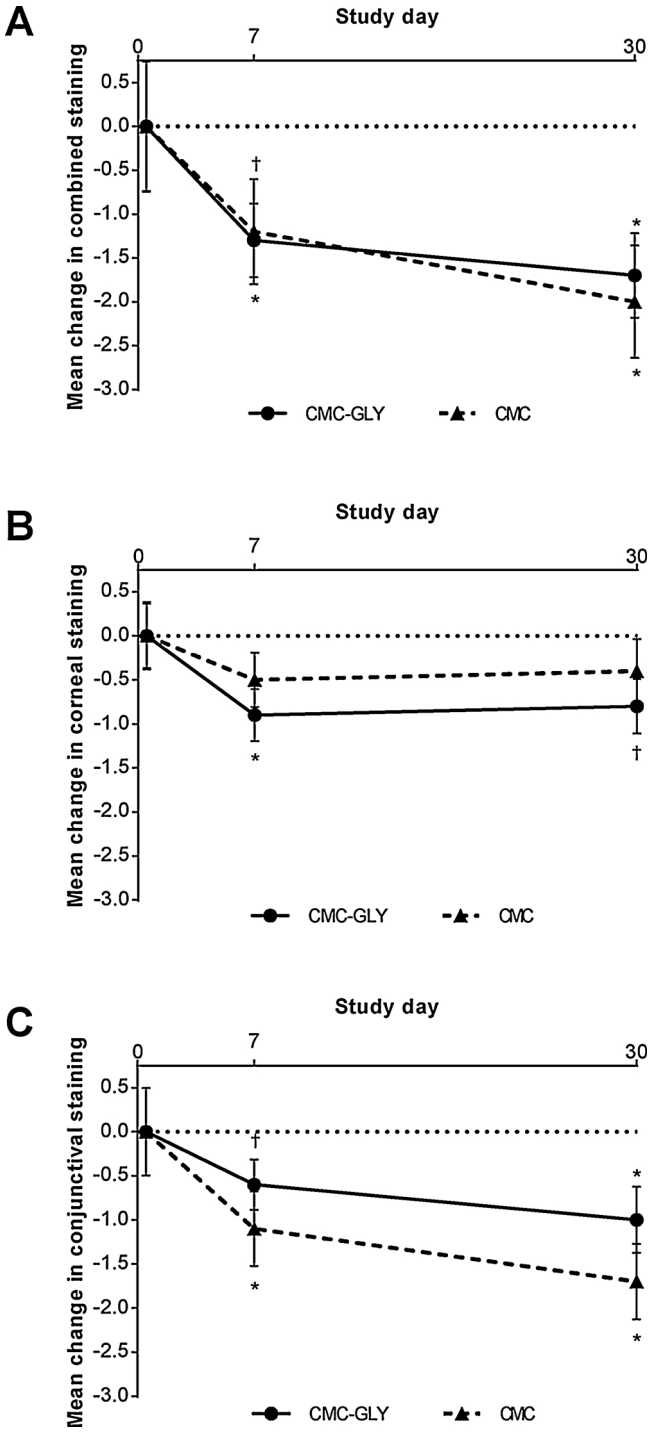

Fig. 4. Change from baseline in (A) combined corneal/conjunctival staining, (B) corneal staining, and (C) conjunctival staining score. Data points represent mean ± standard error mean in the intent-to-treat population; *p < 0.01; †p < 0.05 by Wilcoxon signed-rank test. CMC = carboxymethylcellulose 1.0%, GLY = glycerin 0.9%. CMC-GLY (n = 94, 94, 93) and CMC (n = 94, 93, 91) at baseline, day 7 and 30, respectively. P values represent within-group change from baseline.

Both the CMC-GLY and CMC-only formulations were well tolerated during the study, with similar favorable safety profiles.

The magnitude of the improvement in symptoms, TBUT and Schirmer scores reported in this study are similar to those reported at 4 weeks in dry eye studies that previously investigated CMC-GLY [29,30], and carbomer-based lipid gels and hydroxypropyl guar gel formulations

Table 3
Summary of adverse events reported in the CMC-GLY and CMC treatment groups.

Adverse event type, n (%)	CMC-GLY (n = 94)	CMC (n = 94)
Treatment-emergent adverse events[a]	14 (14.9)	14 (14.9)
Blurred vision	7 (7.4)	5 (5.3)
Conjunctival hemorrhage	1 (1.1)	1 (1.1)
Vital dye staining present in cornea	1 (1.1)	1 (1.1)
Treatment-related treatment-emergent adverse events	8 (8.5)	7 (7.4)
Blurred vision	7 (7.4)	5 (5.3)
Instillation site pruritus	1 (1.1)	0
Meibomianitis	1 (1.1)	0
Ocular discomfort	1 (1.1)	0
Eye irritation	0	1 (1.1)
Eye pruritus	0	1 (1.1)
Instillation site pain	0	1 (1.1)
Lacrimation increased	0	1 (1.1)
Medication residue present	0	1 (1.1)
Visual acuity reduced	0	1 (1.1)
Treatment-emergent serious adverse events	0 (0.0)	1 (1.1)

CMC, carboxymethylcellulose 1.0%; GLY, glycerin 0.9%.

[a] Treatment-emergent adverse events occurring in at least 2 or more subjects overall.

[31].

CMC-GLY was designed for patients with dry eye who require a more viscous lubricating tear for management of their disease. However, the potential for blurred vision with high-viscosity artificial tears can limit the application of more viscous tears to overnight treatment [32]. Despite the potential for higher rates of blurred vision with products exhibiting higher viscosity, in this study the number of subjects who experienced blurred vision was similar between the CMC-GLY (n = 7) and the CMC-only formulation (n = 5). Furthermore, there were no differences between CMC-GLY and CMC-only formulations for the eye drop experience questions related to “no blurring or visual interference” upon immediate application, and “vision is clear and comfortable” within a few days of application. Differences in eye comfort at first application and visual interference within 10 min of application reported by subjects, in favor of CMC, are probably related to the increased viscosity in the CMC-GLY formulation. Nevertheless, this transient discomfort is offset by the earlier improvement in signs and symptoms of dry eye which can be attributed to the presence of glycerin and osmoprotective solutes. It is also worth considering potential discrepancies in objective and subjective assessments of blurred vison in this study.

The inclusion of humectant polymers, such as CMC, in gel-type artificial tears helps lubricate and hydrate the ocular surface, while increasing viscosity and ocular residency time. This allows for the application of gel-type tears during the day and also at night. Viscosity can be enhanced by reducing the salt content (ie. substitution with osmoprotective solutes), which in turn increases the anionic charge strength of CMC, and by the addition of glycerin, which has a synergistic effect [33]. Furthermore, the inclusion of osmoprotectants such as glycerin protects against hyperosmolarity and may help reduce ocular surface damage and visual disturbance [34,35].

. The significant improvements observed with CMC-GLY in terms of OSDI, TBUT and corneal staining at day 7 were achieved with significantly fewer daily doses of CMC-GLY versus CMC alone, which suggests that doubling the CMC content (from 0.5% in the run-in period to 1.0% in both treatment arms) is less important than the addition of glycerin and osmoprotectants.

In this controlled clinical trial, similar overall performance was observed for both formulations. These results emphasize the variability of response by individual dry eye patients; however, the availability of multiple treatment options should benefit practitioners and facilitate an individually-tailored approach to the management of dry eye. The

earlier benefit observed with CMC-GLY and need for less frequent dosing is likely desirable for patients, and may outweigh any potential for discomfort upon initial application for some patients. Further studies could explore patient preference while rheological studies could evaluate viscosity under shear stress in gel-based formulations to determine which components provide optimal performance in terms of symptom improvement and tolerability. A number of osmoprotectants, including L-carnitine and erythritol, have already shown a potential anti-inflammatory effect in corneal epithelial cells under osmotic stress [36]. Additional studies that include measures of markers of cellular stress could help elucidate effects of the additional components in the CMC-GLY formulation. In addition, studies evaluating the effectiveness of the novel lubricant eye gel in specific subpopulations of patients with dry eye may assist eye care practitioners in treatment decisions.

Overall, the new CMC-GLY lubricant eye gel was well tolerated and effective for relief of dry eye signs and symptoms. Acceptability results indicated some transient blur with both CMC-GLY and CMC alone, but otherwise there were no safety concerns and no treatment-related serious adverse events reported. CMC-GLY was noninferior and demonstrated faster improvement compared with the existing CMC-only formulation. These results support the use of CMC-GLY as an effective treatment to reduce signs and symptoms of dry eye disease.

Summary declaration of interest

C Lievens, G Berdy, D Douglass, S Montaquila have received research funding from and/or are consultants for Allergan plc in conjunction with this study. C Carlisle-Wilcox and S Haque are employees of Allergan plc, Irvine, CA. P Simmons and J Vehige were employees of Allergan plc, Irvine, CA at the time the study was conducted. H Lin was an employee of Allergan plc, Irvine, CA at the time the study was conducted and is currently a medical director at Genentech, a company that does operate in the ophthalmology space.

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