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Over the counter (OTC) artificial tear drops for dry eye syndrome (Review)

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[Intervention Review]

Over the counter (OTC) artificial tear drops for dry eye syndrome

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ABSTRACT

Background

Over the counter (OTC) artificial tears historically have been the first line of treatment for dry eye syndrome and dry eye-related conditions like contact lens discomfort, yet currently we know little regarding the overall efficacy of individual, commercially available artificial tears. This review provides a much needed meta-analytical look at all randomized and quasi-randomized clinical trials that have analyzed head-to-head comparisons of OTC artificial tears.

Objectives

To evaluate the effectiveness and toxicity of OTC artificial tear applications in the treatment of dry eye syndrome compared with another class of OTC artificial tears, no treatment, or placebo.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to December 2015), EMBASE (January 1980 to December 2015), Latin American and Caribbean Health Sciences (LILACS) (January 1982 to December 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the US Food and Drugs Administration (FDA) website (www.fda.gov). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 4 December 2015. We searched reference lists of included trials for any additional trials not identified by the electronic searches.

Selection criteria

This review includes randomized controlled trials with adult participants who were diagnosed with dry eye, regardless of race and gender. We included trials in which the age of participants was not reported, and clinical trials comparing OTC artificial tears with another class of OTC artificial tears, placebo, or no treatment. This review did not consider head-to-head comparisons of artificial tears with another type of dry-eye therapy.

Data collection and analysis

We followed the standard methodological procedures expected by Cochrane. Two authors independently screened the search results, reviewed full-text copies for eligibility, examined risk of bias, and extracted data. We performed meta-analysis for trials that compared similar interventions and reported comparable outcomes with sufficient data. We summarized all other included trial results in the text.

Main results

We included 43 randomized controlled trials (3497 participants with dry eye). Due to the heterogeneity of study characteristics among the included trials with respect to types of diagnostic criteria, interventions, comparisons, and measurements taken, our ability to perform meta-analyses was limited. The review found that, in general, there was uncertainty whether different OTC artificial tears provide similar relief of signs and symptoms when compared with each other or placebo. Nevertheless, we found that 0.2% polyacrylic acid-based artificial tears were consistently more effective at treating dry eye symptoms than 1.4% polyvinyl alcohol-based artificial tears in two trials assessing this comparison (175 participants). All other included artificial tears produced contradictory between-group results or found no between-group differences. Our review also found that OTC artificial tears may be generally safe, but not without adverse events. Overall, we assessed the quality of evidence as low due to high risks of bias among included trials and poor reporting of outcome measures which were insufficient for quantitative analysis. Furthermore, we identified an additional 18 potentially eligible trials that were reported only in clinical trial registers with no associated results or publications. These trials reportedly enrolled 2079 total participants for whom no data are available. Such lack of reporting of trial results represents a high risk of publication bias.

Authors' conclusions

OTC artificial tears may be safe and effective means for treating dry eye syndrome; the literature indicates that the majority of OTC artificial tears may have similar efficacies. This conclusion could be greatly skewed by the inconsistencies in study designs and inconsistencies in reporting trial results. Additional research is therefore needed before we can draw robust conclusions about the effectiveness of individual OTC artificial tear formulations.

PLAIN LANGUAGE SUMMARY

Efficacy of over the counter (OTC) artificial tears for dry eye syndrome

Research question

What is the effect of over the counter (OTC) artificial tears on dry eye syndrome?

Background

Dry eye syndrome is a long-term condition that is known to cause eye discomfort and visual disturbances like blurred vision. This condition affects millions of people around the world, and the first-line treatment for dry eye is typically over the counter (OTC) artificial tears. OTC artificial tears are meant to replace or supplement the tears (fluid) that naturally cover the eye's front surface (cornea and conjunctiva). There are a great number of commercially available artificial tears, yet there is currently no agreement about whether one formulation works better than another at treating dry eye. Our review attempts to bridge this knowledge gap.

Study characteristics

This review included 43 randomized controlled trials (3497 people with dry eye) that compared OTC artificial tears with other OTC artificial tears, with no treatment, or with placebo. We considered participant symptoms to be the primary outcome for this review. We recorded other commonly performed dry eye tests as secondary outcomes (e.g. vision, tear stability). We measured primary and secondary outcomes at two and four weeks, although we also considered other time points in this review. We searched for trials up to December 2015.

Key results

This review analyzed many OTC artificial tear formulations, and most of the literature indicates uncertainty as to which OTC artificial tear works best. The literature also shows that OTC artificial tears may be effective at treating dry eye symptoms and that OTC artificial tears are generally safe, although not without side effects.

We also identified an additional 18 potentially eligible trials that were registered, but did not provide any results or publications. These trials may have enrolled 2079 total participants for whom no data are available. Without the results of these trials, the effects of the OTC artificial tears that they evaluated are unknown.

Quality of the evidence

The overall quality of the evidence was low for the various OTC artificial tear formulations compared in this review. This finding indicates that future published research may have an important impact on the conclusions currently provided in this review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Over the counter artificial tear drops for dry eye syndrome

Population: people with dry eye

Setting: home or clinic

Comparison (Intervention vs. comparator)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with comparator	Mean difference (95% CI) Negative values are in favor of intervention; positive values in favor of comparator				
Patient-reported symptoms of dry eye						
1. a) 0.3% carbomer vs. placebo	-	Day 21 or 28: -0.38 (-0.99 to 0.22)	-	297 (2)	⊕⊕⊝⊝ **low**[1,2]	
		Day 56: -0.56 (-1.18 to 0.07)	-	281 (2)		
1. b) 0.5% CMC vs. placebo	See comment	-	-	19 (1)	-	A significant reduction in some unspecified symptoms ($P < 0.05$) in the treatment group reported by trial; no numeric data reported for the placebo group
1. c) 0.6% PG versus placebo	See comment	-	-	49 (1)	-	Outcome not reported
2. PEG 400 + PG + HP-guar vs. CMC	See comment	-	-	471 (6)	-	Improvements in dryness and foreign body sensation favoring PEG/PG/HP guar group at week 6 in one trial; no significant difference

						between groups in four trials; outcome not reported in one trial
3. PEG 400 + PG or sodium hyaluronate vs. HPMC or CMC	See comment	-	-	30 (1)	-	No significant between-group differences in OSDI score reported by trial
4. 0.4% PEG 400 + PG vs. 0.25% PEG 400	See comment	-	-	22 (1)	-	Outcome not reported
5. 0.25% PEG 400 vs.1% CMC	See comment	-	-	104 (1)	-	Significant between-group differences favoring PEG group at week 4 reported by trial
6. 0.25% PEG 400 vs. 0.3% HPMC	See comment	-	-	20 (1)	-	Outcome not reported
7. PEG 400 vs. HP-guar	See comment	-	-	40 (1)	-	Significantly less blurred vision favoring PEG 400 at week 4 reported by trial
8. 0.5% CMC vs. sodium hyaluronate	-	Month 1: 0.93 (-1.39 to 3.25)	-	131 (2)	⊕⊕⊖⊖ **low**[1,2]	One trial did not report this outcome
9. 0.5% CMC vs. 0.3% HPMC	See comment	-	-	268 (3)	-	Insufficient data for between-group comparisons in two trials; outcome data not reported in one trial
10. 0.5% CMC vs 1% CMC	See comment	-	-	103 (1)	-	No significant between-group differences in reduction at day 30 reported by trial
11. lipid-based CMC vs. aqueous-based CMC	See comment	-	-	315 (1)	-	Insufficient data for between-group comparisons
12. Two different concentrations of CMC + hyaluronic acid vs CMC	See comment	-	-	305 (1)		No statistically significant between-group differences in OSDI score; significant between-group difference in dryness favoring one of the CMC + hyaluronic acid formulations over the other formulation at day 90 reported by trial
13. 0.5% CMC vs 0.5% CMC + castor oil vs. 1.0% glycerine + castor oil	See comment	-	-	18 (1)	-	Insufficient data for between-group comparisons

14. 1.0% CMC vs. 0.18% sodium hyaluronate	See comment	-	-	21 (1)	-	Significant between-group difference in comfort favoring hyaluronate group at day 7 reported by trial
15. 1.0% CMC vs. 0.3% HPMC	See comment	-	-	77 (2)	-	Significant improvement in dryness in HPMC, but not CMC treatment period of 4 weeks in one trial; significant improvements in the sum of symptoms favoring CMC group at week 4 and 8 in one trial
16. 1.0% CMC vs. 0.4% carbomer	See comment	-	-	60 (1)	-	Significant between-group differences in symptom favoring carbomer-based gel at month 3 reported by trial
17. 0.2% carbomer vs. 0.3% HPMC vs. 0.3% anhydrous liquid lanolin	See comment	-	-	67 (1)	-	No significant between-group differences in changes from baseline reported by trial
18. 0.2% carbomer vs. HP-guar	See comment	-	-	30 (1)	-	Between-group comparisons not reported
19. 0.3% carbomer vs. 0.18% sodium hyaluronate	See comment	-	-	368 (2)	-	No significant between-group differences at month 1 reported by trials
20. Carbomer gels containing different preservatives	See comment	-	-	179 (1)	-	No significant between-group differences reported by trial
21. 0.2% PAA vs. 1.4% PVA	See comment	-	-	159 (2)	-	Significant improvements favoring PAA over PVA at weeks 3, 4, and 6 reported by 2 trials
22. 1.4% PVA vs. 0.1% sodium hyaluronate	See comment	-	-	35 (1)	-	No significant differences between groups reported by trial
23. 1.4% PVA vs. carbomer	See comment	-	-	55 (1)	-	Significant differences favoring carbomer gel at week 2 reported by trial
24. 0.3% HPMC vs. 0.4% hyaluronic acid	See comment	-	-	113 (1)	-	Significant between-group differences favoring hyaluronic acid at days 15, 30, and 60 reported by one trial

25. Two different products containing 0.3% HPMC	See comment	-	-	37 (1)	-	No significant differences in symptoms observed between treatments reported by one trial
26. 0.3% HPMC with vs without bicarbonate	See comment	-	-	27 (1)	-	Insufficient data for between-group comparisons
27. 0.3% HPMC vs. 1.25% castor oil	See comment	-	-	53 (1)	-	Outcome not reported
28. Trehalose + hyaluronic acid vs. PEG + PG + HP-guar	See comment	-	-	17 (1)	-	Significant between-group difference in impact at work favoring trehalose + hyaluronic acid, but no significant between-group difference in OSDI score

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CMC: Carboxymethylcellulose; **CI:** Confidence interval; **HP:** hydroxypropyl; **HPMC:** hydroxypropyl methylcellulose; **OSDI:** Ocular Surface Disease Index; **PAA:** Polyacrylic acid; **PEG:** Polyethylene glycol; **PG:** Propylene glycol; **PVA:** Polyvinyl alcohol; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for risk of detection bias in included trials (-1)
[2]Downgraded for risk of attrition bias in included trials (-1)
[3]Downgraded for imprecision (-1)

BACKGROUND

Description of the condition

Dry eye is a common disorder of the eye's surface, characterized by the degradation of the fluid layer covering the eye (tear film) and increased eye inflammation. Inflammation is the body's natural restorative and protective response to disease and eye injury. The tear film is composed of two distinct phases: an inner aqueous phase/mucin phase that covers the anterior eye surface (corneal epithelium) and an outer, mostly lipid (fat) phase that interacts with the environment and the aqueous/mucin layer (Lemp 2008; McCulley 1997). Maintaining the structural integrity of these phases involves a complex interaction between the eye and the environment. The degradation of the tear film can be caused by a variety of factors, such as systemic autoimmune diseases (e.g. Sjögren's syndrome), dietary deficiencies, environmental factors (e.g. contact lenses), and dysesthesia (ocular irritation due to loss of corneal innervation after refractive surgery) (DEWS 2007). These factors may lead to decreased tear production, or increased eye inflammation and tissue damage, and ultimately tear film breakdown, all of which can be associated with clinical symptoms (Lemp 2008). Additionally, eye inflammation can inadvertently lead to further dysfunction of the eye's surface and its associated structures (e.g. lacrimal gland), in turn leading to further tear reduction and inflammation (De Paiva 2008; Stern 2004). The etiology of dry eye has had two major classifications: tear deficiency and excessive tear evaporation (Lemp 1995). Common dry eye syndrome symptoms include pain, foreign body sensation, dryness or irritation, burning, light sensitivity, redness, and eyelash debris (Ehlers 2008).

Epidemiology

Dry eye is a prevalent condition worldwide (5.5% to 33.7%), with risk factors including age 50 years and older, refractive surgery, and being female (DEWS 2007; Lemp 2008; Schaumberg 2003; Schaumberg 2009). The reported prevalence varies widely in the epidemiologic literature, based on the wide array of subjective patient-reported symptom questionnaires and objective clinical tools used to assess dry eye. The Women's Health Study, the largest cohort study examining the prevalence of dry eye among 39,876 women, reported a prevalence of 6.1% with a clinical diagnosis; severe dry eye symptoms and at least one dry eye symptom were reported for 3.4% and 9.1% of women, respectively (Schaumberg 2003). In another large, population-based study of 25,444 middle-aged and older men, Schaumberg 2009 reported that 4.43% of men experience dry eye, which translates into 1.68 million American men 50 years and older who experience dry eye compared to 3.23 million women in the same age group (Schaumberg 2003). Many millions more likely experience less severe dry eye symptoms, that may result intermittently from environmental exposure and contact lens use (DEWS 2007). With aging populations in the developed world, and increased frequency of younger adults receiving refractive surgery, dry eye is expected to affect as many as 2.79 million US men by 2030 (Lemp 2008; Schaumberg 2009).

Diagnosis

Current strategies for diagnosing dry eye rely on subjective patient-reported symptoms and objective ocular tests (Korb 2000; Nichols 2000; Perry 2004). However, both strategies have limitations; in some people there is little or no correlation between reported symptoms and ocular surface damage, and there is extreme variation in objective test performance (Lemp 2008; Nichols 2004). The lack of concordance between methods makes it difficult not only to diagnosis people with dry eye, but also to develop treatment regimens for specific disease manifestation and to assess treatment outcomes (Lemp 2008; Nichols 2004).

Treatment options

There are several current treatment options available to people with dry eye, according to the severity of their symptoms. Simple environmental interventions designed to increase air moisture and reduce particles in the air, and nutritional supplements with essential fatty acids, are noninvasive therapies that can improve dry eye-related symptoms in some people (De Paiva 2008; Dogru 2011).

Newer therapies designed to target the inflammatory pathways associated with dry eye include several anti-inflammatory agents such as corticosteroids, cyclosporine A (CsA), nonsteroidal anti-inflammatory drugs (NSAIDS), and tetracycline derivatives (De Paiva 2008; Dogru 2011). For the most severe cases of dry eye more extreme measures are taken, with the application of autologous serum derived from the patient's blood, which supplies additional biochemical nutrients to the ocular surface (Pan 2013), and temporary or permanent blockage of the lacrimal drainage ducts (punctal plugs) to decrease tear drainage (Ervin 2010; Foulks 2003; Quinto 2008).

Description of the intervention

First-line pharmacotherapy for treating dry eye consists of over the counter (OTC) artificial tear drops, gels, ointments, or lubricants (Dogru 2011; Pflugfelder 2007). Manufacturers have developed OTC products that appear to mimic the different layers of the tear film in order to maintain ocular hydration (Perry 2003). Even though these products are referred to as artificial tears, they lack the biologically active components found in natural tears (Dogru 2011; Pflugfelder 2007; Quinto 2008).

One key difference in the many OTC products is the inclusion of chemical formulations, e.g. cellulose ethers, carbomers, polyvinyl alcohol, and lipid-based formulations, which provide additional viscosity and adhesion, and allow for even distribution over the ocular surface (Dogru 2011). Products with an increased viscosity, reserved for those who have not responded to less viscous applications, can lead to blurred vision, thus limiting application to overnight treatment (Perry 2003). Some OTC drops contain tetrahydrozoline (e.g. Visine® Original), which is a medication that constricts blood vessels (vasoconstrictor), and patients often confuse these with artificial tear drops (Soparkar 1997). When used repeatedly, blood vessels will eventually become insensitive, requiring multiple applications over time (Soparkar 1997). Also, artificial tears are typically preserved with chemicals (e.g. benzalkonium chloride (BAK), ethylenediaminetetraacetic acid (EDTA), purite) to avoid bacterial contamination, and they have buffers (e.g. bicarbonate, phosphate) to maintain the normal pH (~ 7.4) of the tear film (Baudouin 2010; Murube 1998). Repeated use of eye drops with preservatives, especially BAK-containing products (e.g. GelTears), is associated with ocular allergies and toxicities (Baudouin 2010; Bron 1998a). These complications can lead to discontinuation of the products and worsening of the condition.

The US Food and Drug Administration (FDA) has designate OTC artificial tears in its *Ophthalmic Drug Products for Over-the-Counter*

Human Use monograph as having specific types of *demulcents* or *emollients* based on their chemical components and not according to clinical effectiveness (FDA 2015). According to the FDA, a *demulcent* is “an agent, usually a water-soluble polymer, which is applied topically to the eye to protect and lubricate mucous membrane surfaces and relieve dryness and irritation.” An *emollient* is "an agent, usually a fat or oil, which is applied locally to eyelids to protect or soften tissues and to prevent drying and cracking.” Table 1 outlines the specific formulations and concentrations permitted by the FDA for OTC *demulcents* and *emollients* (FDA 2015). Other common non-active ingredients used in artificial tears not listed in the FDA monograph include hydroxypropyl-guar, sodium hyaluronate, and castor oil (Dogru 2011; Pflugfelder 2007; Springs 2010). It is important to note that the FDA guidance, when manufacturers follow the aforementioned monography, does not require the manufacturers to conduct human clinical trials to market these products.

How the intervention might work

The primary role of OTC artificial tears is to supplement the patient’s tears and to provide the necessary eye lubrication needed to avoid eye complications; this should in turn help reduce tear evaporation and stabilize the tear film. By doing so, OTC therapy is believed to reduce tear osmolarity, which is associated with the pathogenesis of dry eye-related inflammation (Craig 1997; Foulks 2007: Rashid 2008). Artificial tears have been associated with patient-reported symptom improvement, but they have not been shown to improve the clinical disorder permanently (Peral 2008). However, this fact is in accordance with the FDA’s regulations. Specifically, the FDA indicates that OTC artificial tears are intended to provide “temporary relief of burning and irritation due to dryness of the eye,” and “temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun,” or to be “protectant against further irritation or to relieve dryness of the eye,” and to “prevent further irritation or to relieve dryness of the eye” (FDA 2015). Furthermore, claims about treatment efficacy are not allowed (FDA 2015).

Therapeutic properties observed from artificial tears include stabilization of the tear film, protection of the ocular surface (cornea and conjunctiva), reduced tear evaporation, and enhanced wound healing and lubrication (Lemp 2008). Additional compounds found in artificial tears include chemical preservatives, which are essential for multidose applications to avoid contamination. Such preservatives are known to be associated with allergic reactions, which limit their long-term effectiveness (Baudouin 2010; Dogru 2011). Given the potential for allergic and toxic reactions to the chemical preservatives, artificial tears are now available in single doses, which eliminates the need for preservative; however, single-dose artificial tears are more costly (Pflugfelder 2007).

Why it is important to do this review

Dry eye is the most common eye condition that drives older people to seek medical attention (Schaumberg 2009). In addition to their widespread prevalence, dry eye-related symptoms and vision impairment have a significant impact on quality of life (Friedman 2010). Given that there are different formulations allowed by the FDA, there is no consensus on which artificial tears offer the most improvement in dry eye-related symptoms. We do not know whether any of the ingredients or specific formulations are actually associated with improved clinical outcomes. Conducting a systematic review of the highest quality evidence on a variety of available OTC artificial tear products, using common experimental study designs and outcome assessment, will provide a better understanding of the effectiveness of these products.

OBJECTIVES

To evaluate the effectiveness and toxicity of OTC artificial tear applications in the treatment of dry eye syndrome compared with another class of OTC artificial tears, no treatment, or placebo.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized or quasi-randomized controlled trials.

Types of participants

We included trials of adult participants with dry eye as defined by the trial investigators. We also included trials in which the age of participants was not reported. We applied no restrictions on race or gender.

Types of interventions

We included trials comparing OTC artificial tears with another class of OTC artificial tears, placebo (e.g. saline or vehicle), or no treatment. We have not included head-to-head comparisons of artificial tears with another type of dry eye therapy (corticosteroids, CsA, autologous serum, NSAIDs, tetracyclines, or essential fatty acid supplements), because many of these alternative therapies cannot be obtained over the counter, some of them are not topically applied, and many of them have pharmacologically active ingredients. We also excluded contact lens wearers, because contact lenses can be an external instigator of dry eye, which may resolve after removing the contact lenses.

Types of outcome measures

Primary outcomes

The primary outcome of this review was between-group, participant-reported changes in frequency and severity of dry eye symptoms, as reported in the included trials at two and four weeks of follow-up. We excluded trials in which the follow-up period was less than one week. We also analyzed outcomes at other time points after one week or more, as reported in the included trials.

Secondary outcomes

The secondary outcomes of this review included objective physical examination, diagnostic tests, and vision-related outcomes as described below:

- Schirmer’s test (with or without anesthesia): mean change in millimeters at two and four weeks
- Tear film break-up time (TBUT): mean change in tear film break-up time in seconds at two and four weeks
- Ocular surface staining with fluorescein: mean change in total score from baseline to follow-up at two and four weeks
- Ocular surface staining with rose bengal: mean change in total score from baseline to follow-up at two and four weeks

- Ocular surface staining with lissamine green: mean change in total score from baseline to follow-up at two and four weeks
- Osmolarity: mean change in mOsmol/L from baseline to follow-up at two and four weeks
- Best-corrected visual acuity (BCVA):
  - Mean change from baseline to two and four weeks of follow-up (with the Snellen chart or its equivalent)
  - The proportion of participants with one or more lines of improvement on the Snellen chart or its equivalent if measured with a different chart
  - The proportion of participants with 20/20 acuity or better at two and four weeks
  - The proportion of participants with 20/40 acuity or better at two and four weeks
- Contrast sensitivity: mean change from baseline to two and four weeks

We present secondary outcomes measured at additional follow-up visits as reported in the included trials.

Adverse outcomes

We compared adverse effects as reported in the included trials. We also assessed adherence to treatment protocols and treatment abandonment if associated with any adverse effect of treatment.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (Cochrane Central Register of Controlled Trials, which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to December 2015), EMBASE (January 1980 to December 2015), Latin American and Caribbean Health Sciences (LILACS) (January 1982 to December 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the US Food and Drugs Administration (FDA) website (www.fda.gov). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 4 December 2015.

See appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6), ICTRP (Appendix 7) and the FDA website (Appendix 8).

Searching other resources

We also searched reference lists of the trials included in this review to identify additional potentially relevant trials.

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of all records identified through the searches. Each review author classified each study as 'relevant', 'potentially relevant', or 'definitely not relevant.' We then retrieved full-text reports of the studies assessed as relevant or potentially relevant. Two review authors independently assessed the eligibility for inclusion of the full-text reports and classified each as 'include', 'unclear', or 'exclude'. We resolved any discrepancies through discussion, and the third review author adjudicated on the assessments when discrepancies were not resolved. One review author also contacted trial investigators for additional clarification when studies were assessed as unclear. We report studies excluded after full-text assessment in the Characteristics of excluded studies table, with reasons for exclusion.

Data extraction and management

Two review authors independently extracted pertinent trial-level characteristics, including descriptions of the participant sample, study design, treatment comparisons, and treatment outcomes from the included trials using data extraction forms developed by Cochrane Eyes and Vision. We resolved discrepancies through discussion. One review author attempted to contact investigators of included trials for missing data, with a period of three weeks for the trial investigators to respond. One review author entered data into Review Manager 5 (RevMan 2014) and a second review author confirmed all entries.

Assessment of risk of bias in included studies

Two review authors independently assessed the methodological characteristics of the included trials as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We evaluated the following 'Risk of bias' domains:

- Selection bias (sequence generation and allocation concealment);
- Performance bias (masking of trial participants and trial personnel);
- Detection bias (masking of outcome assessors);
- Attrition bias (incomplete outcome data);
- Reporting bias (selective outcome reporting);
- Other sources of bias.

Review authors judged each domain as low risk, high risk, or unclear risk of bias with documentation to support the review authors' judgment. There were additional methodological considerations for the risk of bias of cross-over clinical trials, including whether there was a washout period, whether the number lost to follow-up after each phase was reported, and whether the data are reported for each phase or by treatment, as outlined in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). One review author attempted to contact the primary trial investigator if there was insufficient information to determine the risk of bias. We resolved discrepancies through discussion.

Measures of treatment effect

We calculated summary risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (the proportion of participants reporting improvement in ocular staining fluorescein and the proportion of participants who reported adverse events) if sufficient data were provided. We calculated standardized mean differences for continuous scales of patient-reported outcomes to account for the variation in measurement scales. We summarized continuous data from objective ocular tests by calculating mean differences with 95% CIs from baseline to follow-up between the

treatment and control arms (ocular surface staining, Schirmer's test, and tear film break-up time) if sufficient data were provided regarding within- and between-group differences. If we determined that there was a significant carry-over effect in the cross-over clinical trials by reviewing the information about the evaluation of carry-over effect in the trial reports, the review authors planed to analyze the first-phase data as a parallel design and perform sensitivity analysis, given the high risk of bias for incomplete outcome reporting, as per Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). None of the cross-over clinical trials included in this review, however, reported the data in the first phase separately from the second phase.

Unit of analysis issues

The unit of analysis in this review was an individual participant who was randomized to each treatment arm, because dry eye is usually bilateral. When both eyes of a single participant were randomized to one treatment and each eye of a single participant was included in the analyses separately for evaluating eye-specific outcomes, the review authors classified the trial as cluster-randomized. The review authors planned to include such a trial design in analysis by applying additional methods described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), but only when intra-person correlation was considered in their analyses. However, the included trial with this design did not address intra-person correlation, so we did not include this trial in the analysis.

Dealing with missing data

The review authors attempted to contact investigators of included clinical trials for clarification of criteria for assessing risk of bias as mentioned above, and for missing primary and secondary outcome data. We extracted available data from the published papers whenever trial authors were unable to provide information on missing data or did not respond after a period of three weeks.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by examining characteristics of trial participants, treatment/control comparisons, and assessment of primary and secondary outcomes. We examined consistency across trials with the I^2 statistic and by inspection of forest plots to determine the presence of heterogeneity. We interpreted an I^2 statistic value greater than 50% as an indication of considerable statistical heterogeneity. In that case we did not report a pooled estimate. In addition, we did not present a pooled estimate when we detected clinical or methodological heterogeneity from the details shown in the Characteristics of included studies table. Instead, we reported a narrative or tabulated summary of the included trials.

Data synthesis

We provided a narrative summary when we detected clinical or methodological heterogeneity, due to variability in interventions, measurements taken, and follow-up intervals for the primary and secondary outcomes of interest. We conducted a random-effects meta-analysis only when there was clinical, methodological, and statistical homogeneity among the included trials. When a meta-analysis included fewer than three trials, we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We did not perform any subgroup analysis because there were insufficient data. If subgroup analysis is considered in future updates of this review, we will stratify the results by the underlying etiology of dry eye symptoms, including tear deficiencies (Sjögren's syndrome), evaporative dry eye (blepharitis or meibomian gland dysfunction), and participants with Stevens-Johnson syndrome. Additional subgroups will include level of adherence throughout follow-up, and preservatives found in artificial tear applications.

Sensitivity analysis

We did not conduct sensitivity analyses to determine the impact of trials at high risk of bias, cross-over trials, industry-funded trials, and unpublished trials, because this review did not include a sufficient number of trials for analysis.

"Summary of findings"

We prepared a "Summary of findings" table for the primary outcome of this review. Two review authors independently graded the quality of evidence for each outcome using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) classification (www.gradeworkinggroup.org/). We resolved discrepancies by discussion and consensus within the review team. For each outcome, we graded the quality of evidence as high, moderate, low, or very low using the following criteria to downgrade the assessment.

- High or unclear risk of bias among included trials.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results (i.e. wide confidence intervals).
- High probability of publication bias.

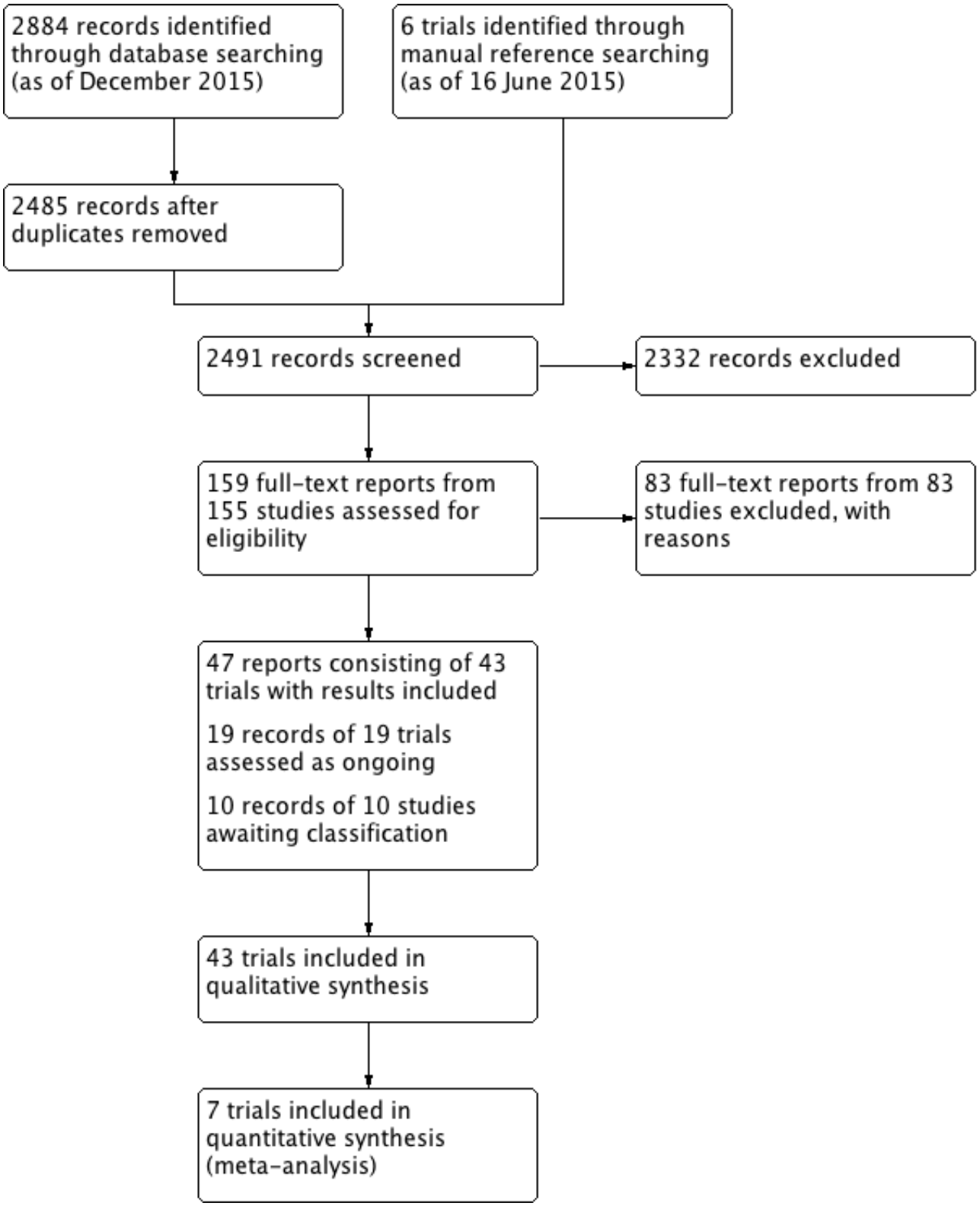
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 2884 records as of December 2015 (Figure 1). We identified an additional six trials after searching reference lists. After deduplication we screened 2491 records, and assessed 159 reports from 155 unique studies as relevant or potentially relevant. Of the 159 full-text reports assessed, we included 47 reports of 43 completed trials (two reports each from six trials; one report consisted of three trials (Donshik 1998 Trial 1; Donshik 1998 Trial 2; Donshik 1998 Trial 3)), identified 19 reports of 19 potentially relevant ongoing trials, excluded 83 reports of 83 studies, and classified 10 records of 10 studies as awaiting classification. The 10 studies awaiting classification were only reported in clinical trial registers or published in a language not read by the authors. We will include additional information about these studies in future updates of this review.

Figure 1. Flow diagram.



Included studies

We included 43 trials in this review. Table 2 presents a summary of study design, trial participants, interventions, and follow-up periods for the included trials. Six trials (Christensen 2009; Foley-Nolan 1995; Huth 2008; Kislan 2008; Lanz 2006; Simmons 2004a) were published in abstract form only. The included trials were published between 1988 and 2015. Of the 43 trials, 34 had a parallel-group design, eight trials used a cross-over design, and

we classified one trial as cluster-randomized because participants were randomized to interventions and both eyes of single participant were analyzed. Overall, 3497 participants were enrolled in the included trials, ranging from 19 to 315 participants in each trial. Follow-up periods ranged from one week to three months.

The interventions investigated varied across the included trials. Table 3 presents a summary of interventions and comparisons. All but six trials (Aguilar 2014; Benelli 2010; Garcia-Lazaro 2011; Huth 2008; Khanal 2007; Simmons 2004a) assessed subjective dry eye symptoms. Objective physical examination and diagnostic tests, including Schirmer's test, TBUT, ocular staining, and osmolarity, were performed in all trials except Simmons 2004a. Thirty (69.8%) trials reported adverse events.

Excluded studies

We excluded 83 studies after full-text assessment. They are listed in the Characteristics of excluded studies table, with reasons for exclusion. Of the 83 excluded studies, 34 studies did not evaluate an intervention of interest; 19 studies were not randomized controlled trials; 18 studies were reported only in clinical trial registers with no associated results or publications; eight studies did not evaluate study participants eligible for this review; and the remaining four studies were overviews of previously published clinical trials with no original data.

The 18 studies that were reported only in clinical trial registers with no associated results or publications potentially enrolled 2079 total participants.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is shown in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

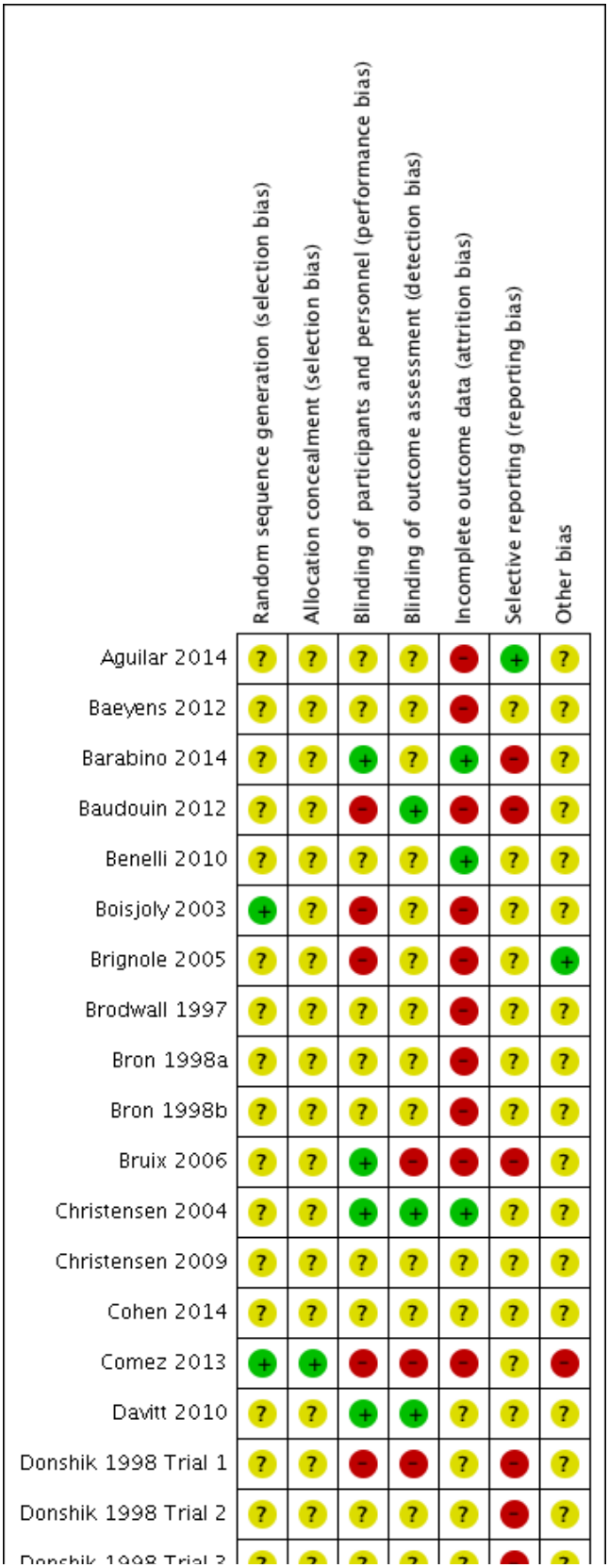
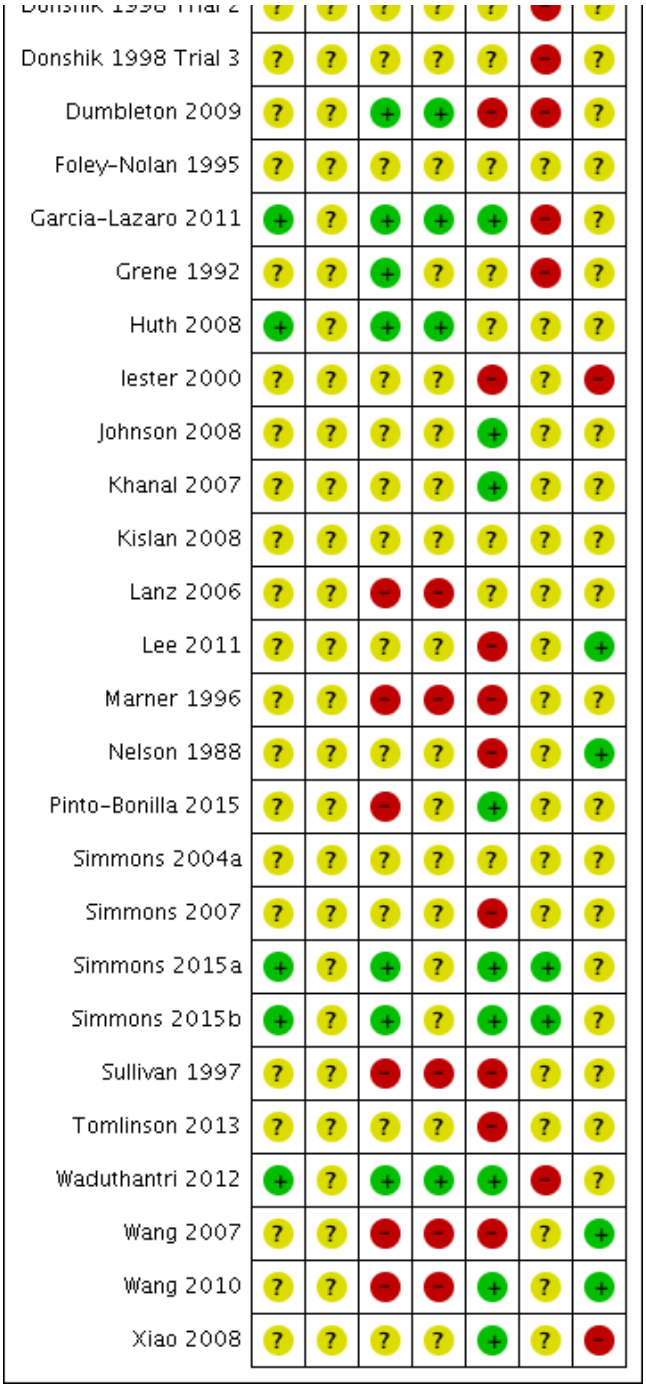


Figure 2. (Continued)



Allocation

Sequence generation

We assessed seven (16%) trials to be at low risk of bias as they employed adequate methods of sequence generation: three trials employed random number tables (Boisjoly 2003; Comez 2013; Garcia-Lazaro 2011); three trials (Huth 2008;Simmons 2015a; Simmons 2015b) used computer software to generate a random sequence; and Waduthantri 2012 used a simple randomization process for picking the participants for each group from 30 masked stubs. Thirty-six (84%) trials did not clearly report how random sequences were generated.

Allocation concealment

We assessed one (2%) trial to be at low risk of bias; in Comez 2013, trial personnel were prevented from seeing the assignment before and until they were assigned by using sequentially-numbered containers. The remaining 42 (98%) trials did not describe the method of allocation concealment, or reported insufficient detail to permit judgment of this parameter.

Masking (performance bias and detection bias)

In six (14%) trials, masking of participants, trial personnel, and outcome assessors was adequately performed (Christensen 2004; Davitt 2010; Dumbleton 2009; Garcia-Lazaro 2011; Huth 2008; Waduthantri 2012); we therefore assessed these six trials to be at low risk of performance and detection bias.

Twenty trials were reported as being double-masked (Baeyens 2012; Bron 1998a; Christensen 2009; Cohen 2014; Johnson 2008; Nelson 1988; Tomlinson 2013), single-masked (Foley-Nolan 1995), masked (Simmons 2007), masked-observer (Lee 2011) or investigator-masked trials (Aguilar 2014; Benelli 2010; Brodwall 1997; Bron 1998b; Donshik 1998 Trial 2; Donshik 1998 Trial 3; Khanal 2007; Kislan 2008; Simmons 2004a; Xiao 2008), but insufficient details were provided as to how masking was performed. Iester 2000 did not report masking. We classified these 21 (49%) trials as being at unclear risk of performance and detection bias.

We assessed four (9%) trials at low risk of performance bias for masking participants and trial personnel, but unclear risk of detection bias for not reporting whether outcome assessors were masked (Barabino 2014; Grene 1992; Simmons 2015a; Simmons 2015b). We assessed three (7%) trials at high risk of performance bias for lack of masking participants and trial personnel, but unclear risk of detection bias for not reporting whether outcome assessors were masked (Boisjoly 2003; Brignole 2005; Pinto-Bonilla 2015). In Bruix 2006 participants and trial personnel were masked (low risk), but outcome assessors were not masked (high risk). In Baudouin 2012, masking of participants was not performed (high risk), but trial personnel and outcome assessors were masked (low risk).

Five trials were open-label studies (Donshik 1998 Trial 1; Lanz 2006; Marner 1996; Wang 2007; Wang 2010). In Sullivan 1997 and Comez 2013, participants were masked, but participating investigators and outcome assessors were not masked. We classified these seven (16%) trials as being at high risk of performance and detection bias.

Incomplete outcome data

We present numbers of participants who were excluded after randomization or lost to follow-up in each trial in the Characteristics of included studies table. We rated the risk of bias as low when an intention-to-treat (ITT) analysis was performed. We judged whether the trial followed ITT analysis or not based on the following three principles; 1) keeping participants in the intervention groups to which they were randomized, regardless of the intervention they actually received; 2) measuring outcome data on all participants; and 3) including all randomized participants in the analysis (Higgins 2011a).

Twelve (28%) trials were at low risk of bias for this parameter (Figure 2). We rated 12 (28%) trials as unclear risk of bias for this parameter because the numbers randomized into each intervention group were not clearly reported. We assessed the remaining 19 (44%) trials to be at high risk of bias for this parameter.

Selective reporting

Only six (14%) trials (Aguilar 2014; Baeyens 2012; Christensen 2009; Simmons 2015a; Simmons 2015b; Waduthantri 2012) had published protocols or registered their trials prior to publishing the results of their trials. Of these six trials, all prespecified outcomes were reported in Aguilar 2014,; Simmons 2015a, Simmons 2015b (low risk); secondary outcomes were not presented in the protocol in Baeyens 2012 (unclear risk); results from Christensen 2009 were only reported in a conference abstract (unclear risk); and not all pre-specified outcomes in the protocol were reported in the final paper in Waduthantri 2012 (high risk). We rated 28 (65%) trials as unclear risk of bias due to insufficient information to permit judgment. One trial (Dumbleton 2009) claimed that results for the objective signs were not described in the paper because no notable clinical occurrences or adverse events were observed; we assessed this trial to be at high risk of bias for selective reporting. We rated the remaining eight trials at high risk of bias because they did not fully report at least one outcome and/or the specified follow-up time described in the Methods sections of the articles.

Other potential sources of bias

We found no other potential sources of bias in five (12%) trials (Brignole 2005; Lee 2011; Nelson 1988; Wang 2007; Wang 2010), but we identified at least one of the following potential sources of bias in the remaining 38 trials (88%):

- Twenty (47%) trials were funded by industry or materials were supplied by industry (Barabino 2014; Baudouin 2012; Benelli 2010; Boisjoly 2003; Donshik 1998 Trial 1; Donshik 1998 Trial 2; Donshik 1998 Trial 3; Dumbleton 2009; Grene 1992; Iester 2000; Johnson 2008; Kislan 2008; Khanal 2007; Pinto-Bonilla 2015; Simmons 2004a; Simmons 2015a; Simmons 2015b; Sullivan 1997; Tomlinson 2013; Waduthantri 2012).
- Fourteen (33%) trials had at least one of the authors affiliated with industry (Baeyens 2012; Baudouin 2012; Brodwall 1997; Bron 1998b; Christensen 2004; Christensen 2009; Cohen 2014; Davitt 2010; Iester 2000; Khanal 2007; Pinto-Bonilla 2015; Simmons 2007; Simmons 2015a; Simmons 2015b).
- Baseline values were not equivalent in seven (16%) trials (Aguilar 2014; Benelli 2010; Bron 1998a; Bruix 2006; Dumbleton 2009; Sullivan 1997; Waduthantri 2012).
- Eight (19%) trials used a cross-over design, of which five had a washout period between the two study phases (Boisjoly 2003; Garcia-Lazaro 2011; Huth 2008; Pinto-Bonilla 2015; Tomlinson 2013). Marner 1996 did not have a washout period, but they assessed carry-over and period effects. Two trials did not report whether or not there was a washout period (Kislan 2008; Lanz 2006).
- Unit-of-analysis errors occurred in Xiao 2008 and Comez 2013; the unit of randomization (individual) was different from the unit of analysis (eye), and non-independence of eyes was not addressed in the analysis. In Comez 2013, each eye of a single participant was assigned to different artificial tears, and the two eyes of each participant were considered to be independent data in the analysis.
- In six (14%) trials, participants were allowed to use additional artificial tears as needed (Benelli 2010; Bron 1998a; Bruix 2006; Dumbleton 2009; Sullivan 1997; Waduthantri 2012). In one trial (Johnson 2008), participants were instructed to use the tear substitutes from two to eight times per day. In one trial (Sullivan 1997), participants who required more than six instillations per day were withdrawn from the trial and were considered as treatment failures.
- One trial (Dumbleton 2009) did not have a washout period before the intervention, even though the trial participants were

regular users of ocular lubricants, and in another trial (Brodwall 1997) only current drop users had a washout before they started the intervention.

- Christensen 2004 excluded participants if they had low corneal staining scores at baseline.
- Participants were stopped at different time points in one trial (Iester 2000).
- Six (14%) trials were published in abstract form only (Christensen 2009; Foley-Nolan 1995; Huth 2008; Kislan 2008; Lanz 2006; Simmons 2004a).

Effects of interventions

See: **Summary of findings for the main comparison**

1. a) 0.3% carbomer ophthalmic gel versus placebo (two trials)

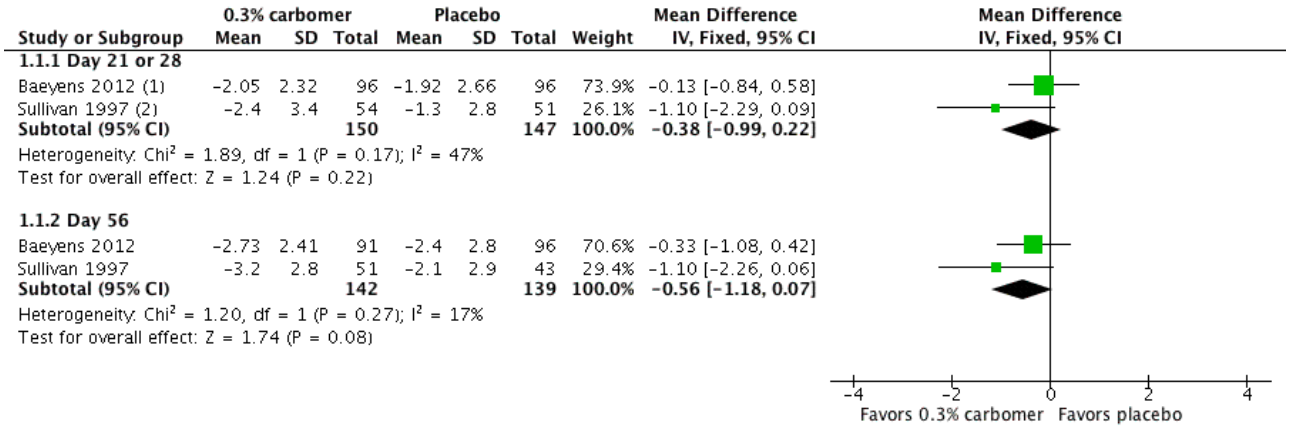
One two-arm trial (Sullivan 1997) and one three-arm trial (Baeyens 2012) compared 0.3% carbomer ophthalmic gel with placebo. Baeyens 2012 included 0.18% sodium hyaluronate in their other arm. In Sullivan 1997's eight-week trial, 62 and 61 participants with moderate to severe dry eye were randomized into the carbomer group or the placebo (mannitol vehicle) group, respectively. Eleven participants (17.7%) in the carbomer group and 19 participants (31.1%) in the placebo group were excluded or lost to follow-up. In this trial, participants who required instillations more than six times per day were excluded from the trial because they were considered treatment failures. A greater proportion of men were enrolled in the carbomer gel group compared with the placebo group. In Baeyens 2012's three-month trial, 304 participants with moderate dry eye were randomized (97 to the carbomer group; 101 to the placebo (saline) group; 106 to the sodium hyaluronate group), and all except one participant in the carbomer group were included in the intention-to-treat analysis. The worst eye (Schirmer's test) was selected for analysis in both trials.

Primary outcomes

In Sullivan 1997, dryness, foreign body sensation, tearing, and photophobia were evaluated by using a four-point grading scale, and itching was reported by using a five-point grading scale at 0, 10, 21, 42 and 56 days. Additionally, subjective dry eye symptoms (burning or stinging, blurriness or filminess, dryness or sandiness, stickiness or matted lashes, and itchiness) were assessed with a 10-point grading scale at each visit. Detailed data were presented for dryness and tearing. In Baeyens 2012, the sum of frequency scores (ranging from 0 to 15) for soreness, scratchiness, dryness, grittiness, and burning (each graded on a 0 to 3 scale) were assessed at days 28, 56, and 84.

At days 21 or 28 (MD -0.38, 95% CI -0.99 to 0.22) and day 56 (MD -0.56, 95% CI -1.18 to 0.07), the difference in symptom scores when comparing 0.3% carbomer ophthalmic gel with placebo was about one point (Analysis 1.1; Figure 3; Summary of findings for the main comparison). We used the GRADE system to judge the quality level of the body of evidence, and downgraded the findings from high to low quality because the subjective outcome had a lack of masking and there were high losses to follow-up in the included trials.

Figure 3. Forest plot of comparison: 2 Comparison: 0.3% carbomer versus placebo, outcome: 2.1 Mean change in symptom scores.



Footnotes
(1) placebo = saline
(2) placebo = mannitol vehicle

Secondary outcomes

Sullivan 1997 evaluated Schirmer's test, TBUT, and ocular staining with fluorescein and rose bengal at each study visit. No numeric data were available to perform meta-analysis (only P values reported). The change from baseline between groups was significantly better for the carbomer group ($P < 0.05$), for rose bengal staining at days 10, 42 and 56 and for TBUT at days 10 and 21. The trial authors reported that neither between- nor within-group differences were observed for Schirmer's test scores or for fluorescein staining scores. Baeyens 2012 evaluated Schirmer's test, TBUT, ocular staining with lissamine green (summed scores ranging from 0 to 12), and fluorescein staining (global score of type and extent ranging from 0 to 7) at each visit, and they found that there were no significant differences in mean change from baseline between groups for any of these outcomes. Neither trial observed significant visual acuity changes.

Adverse events

Sullivan 1997 observed five participants (8.1%) in the carbomer group who experienced treatment-related ocular adverse events, which included local allergic reaction, mild hyperemia, and mild foreign body sensation. They also noted four participants (6.5%) in the carbomer group and two (3.3%) in the placebo group discontinued the trial because of adverse events. Baeyens 2012 observed five ocular adverse events and seven general disorder or administration site conditions, of which four were reported as serious. Baeyens 2012 also found that 55.2% of the participants in the carbomer group and 15.4% in the placebo group experienced blurred vision at day 84.

1. b) 0.5% carboxymethylcellulose (CMC) versus placebo (one trial)

Bruix 2006 compared 0.5% carboxymethylcellulose-based (CMC) artificial tears with balanced saline solution (placebo group). Thirteen participants in this trial were randomized to the CMC group, and six to the placebo group. This trial did not explicitly report the number of participants who were included in the final analysis at 12 months.

Primary outcomes

The trial assessed 12 subjective dry eye symptoms at baseline and at the end of the trial. The trial authors reported that there was a significant reduction in some unspecified symptoms ($P < 0.05$) in the treatment group. This trial did not report numeric data for the placebo group.

Secondary outcomes

Schirmer's test, ocular fluorescein staining, ocular rose bengal staining, and TBUTs were evaluated, but there were insufficient data to perform within- and between-group comparisons. Schirmer's test values improved in 34.8% of participants in the CMC group, while 25% of participants in the placebo group showed improvement. All participants in the treatment group showed improvement in ocular fluorescein staining, while the placebo group showed no improvement. The treatment group (50%) showed greater improvement than the placebo group (33.3%) when analyzing ocular rose bengal staining, but this difference was not reported to be significant. The treatment group (50%) showed greater improvement for TBUT compared with the placebo group (16.6%).

Adverse events

No adverse events were observed in this trial.

1. c) 0.6% propylene glycol (PG) versus placebo (one trial)

In a one-month randomized controlled trial, Aguilar 2014 compared a 0.6% propylene glycol-based (PG) artificial tear (Systane® Balance) with placebo (saline). Of the 51 participants who were randomized, 49 participants (96.1%; 25 in the PG group and 24 in the saline group) completed the trial.

Primary outcomes

Patient-reported dry eye symptoms were not assessed in this trial.

Secondary outcomes

TBUT, corneal fluorescein staining, and conjunctival lissamine green staining were evaluated at two and four weeks after initiation of treatment. TBUT increased from baseline by 2.83 ± 0.74 seconds in the PG group and 0.66 ± 0.55 seconds in the placebo group at week four. The improvement was significantly greater in the PG group compared with the saline group (MD 2.17 seconds, 95% CI 1.79 to 2.54). We judged the quality of evidence as moderate, downgrading (-1) for unclear risks of bias in the included trial.

The sum of five corneal regions and the sum of six conjunctival regions were separately evaluated with a four-point grading scale in each region. At week four, the sum corneal staining scores were significantly decreased compared with baseline in both groups (MDs -1.16 and -0.13 in the PG group and the placebo group, respectively); these differences were significantly greater in the PG group (MD -1.04, 95% CI -1.43 to -0.64). We judged the quality of evidence as moderate, downgrading (-1) for unclear risks of bias in the included trial.

Conjunctival staining scores showed a similar trend. Sum conjunctival staining scores significantly improved in both groups at week four (MDs -7.52 and -1.83 in the PG group and the placebo group, respectively), and this improvement was significantly greater in the PG group than in the placebo group (MD -5.69, 95% CI -7.44 to -3.93). We judged the quality of evidence as moderate, downgrading (-1) for unclear risks of bias in the included trial.

Adverse events

No adverse events were observed during the trial.

2. Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium (six trials)

Six trials compared a PEG 400, PG, and HP-guar-based ophthalmic gel with a CMC-based eye drop for treating dry eye (Benelli 2010; Christensen 2004; Christensen 2009; Cohen 2014; Davitt 2010; Waduthantri 2012). Four trials used 0.4% PEG 400 and 0.3% PG (Christensen 2004; Christensen 2009; Cohen 2014; Waduthantri 2012); concentrations of PEG 400 and PG were unspecified in Benelli 2010 and Davitt 2010. All trials used 0.5% CMC except Cohen 2014, which used 1.0% CMC. One three-arm trial (Benelli 2010) included another arm investigating 2.5% PEG 400 and sodium hyaluronate. The study duration was six weeks in all trials except Benelli 2010, which was four weeks long. Waduthantri 2012 and Benelli 2010 randomized 30 and 60 participants respectively, who were all included in the final analysis. Christensen 2004 randomized 87 participants and 84 of them (96.6%) completed the trial. Cohen 2014 reported that all 147 participants who were randomized were included in the intention-to-treat analysis; however, it was unclear how the missing data for 10 participants (6.8%) who discontinued the trial were handled, as the authors stated that missing data were not recorded. Christensen 2009 and Davitt 2010 did not explicitly report the number of participants who were randomized, excluded, or lost to follow-up, but each of their final analyses included 105 participants. Christensen 2009 was only published in abstract form.

Primary outcomes

Five trials reported subjective dry eye symptoms as final mean scores or mean change in scores from baseline, although outcome definitions and measurements varied among trials (Christensen

2004; Christensen 2009; Cohen 2014; Davitt 2010; Waduthantri 2012). Christensen 2004 used patient-reported symptoms (burning, stinging, blurry, gritty, dry, scratchy and foreign body sensations) that were measured at days seven and 42 with a Likert-format scale that ranged from strongly disagrees (1) to strongly agrees (5). Christensen 2009 used a Treatment Satisfaction Questionnaire and VF-14 Questionnaire. Cohen 2014 used the Patient Global Assessment of Improvement, Impact of Dry Eye on Everyday Life (IDEEL), Single Symptom Comfort Scale, and Ocular Symptoms Questionnaire to evaluate dry eye symptoms. In Davitt 2010, six patient-reported symptoms of dry eye (dryness, gritty/sandy sensation, burning, redness, crusting on eyelashes, and eyes sticking shut in the morning) were evaluated at baseline and weeks one, two, four and six after treatment by using a five-point grading scale. Participants in Davitt 2010 also completed an Ocular Surface Disease Index (OSDI) questionnaire at baseline and at week six. Waduthantri 2012 used the Symptom Assessment in Dry Eye (SANDE) Score to quantify the frequency and severity of dry eye symptoms (100 mm visual analog scale that ranged from rarely or very mild to all the time or very severe). We could not perform meta-analysis due to heterogeneity in outcome definitions and measurements, and insufficient data provided.

In Christensen 2004, mean agreement to dryness was significantly lower (i.e. improvement in dryness) in the PEG 400/PG/HP-guar group than in the 0.5% CMC group at the end of the trial for dryness in the morning (MD -0.6, 95% CI -1.1 to -0.1), and for dryness at the end of the day (MD -0.6, 95% CI -1.1 to -0.1). Authors also reported significantly lower frequency of foreign body sensation in the PEG 400/PG/HP-guar group compared with the 0.5% CMC group (P = 0.033). Christensen 2009 reported that there were no significant differences in symptoms between the two treatment groups, although both groups showed significant improvement from baseline at week six. Cohen 2014 claimed that 85% of participants in the PEG/PG/HP-guar group and 74% of participants in the CMC group reported improvement in dry eye symptoms based on the Patient Global Assessment of Improvement test (P = 0.14). There were no significant differences in the mean change from baseline scores between the treatment groups at six weeks for the overall Single Symptom Comfort Scale questionnaire (MD -0.50, 95% CI -1.13 to 0.13); they found the same for dryness (MD 0.10, 95% CI -0.26 to 0.46), gritty or sandy sensation (MD 0.10, 95% CI -0.26 to 0.46), burning sensation (MD 0.10, 95% CI -0.22 to 0.42), redness (MD 0.20, 95% CI -0.14 to 0.54), and crusting on the lashes (MD -0.20, 95% CI -0.62 to 0.22). In Davitt 2010, of the six symptoms assessed, improvements in dryness, gritty or sandy sensation and burning were reported as significant compared with baseline values at week six in both intervention groups. Mean OSDI scores at week six showed significant improvement from baseline in the PEG/PG/HP-guar group (MD -8.6 score; P = 0.001) and in the CMC group (MD -10.9; P < 0.0001), but significant differences were not observed between groups (MD 4.4; P = 0.25). In Waduthantri 2012, the symptoms scores showed a significant improvement in both treatment groups at six weeks (P < 0.001), but no significant between-group differences in mean change from baseline symptom scores were observed at six weeks (MD -4.32, 95% CI -24.39 to 15.75). Benelli 2010 did not assess patient-reported changes in dry eye symptoms.

Secondary outcomes

Two trials (Benelli 2010; Waduthantri 2012) conducted Schirmer's test. Summary estimates showed that there was no significant difference in mean change in Schirmer's test values between the two treatment groups at weeks three or four (MD -0.55, 95% CI -1.94 to 0.83; 70 participants) (Analysis 2.1). We graded the quality of evidence as low for this outcome, because there was a high risk of selective outcome reporting bias detected in the included trials, and wide confidence intervals were detected.

All trials except Christensen 2004 assessed TBUT, but data were insufficient for meta-analysis in three of the trials (Christensen 2009; Cohen 2014; Davitt 2010). The remaining two trials (Benelli 2010; Waduthantri 2012) provided sufficient data; however, they did not report this outcome at the same time points; we therefore have not presented a pooled estimate for this outcome (Analysis 2.2). In Benelli 2010, both treatment groups showed significant improvement in mean TBUT values at day 30, but there were no significant between-group difference. The other four trials reported that there were no significant between- and within-group differences in mean TBUT values.

All trials performed corneal fluorescein staining. In three trials (Christensen 2004; Cohen 2014; Davitt 2010), corneal fluorescein staining was measured at baseline and one, two, four and six weeks by applying the National Eye Institute's grading scale (sum of five areas ranging from 0 (normal) to 3 (severe) in each area). The data in Christensen 2004 were insufficient for meta-analysis because they did not report precision measures; however, they did report a significant reduction from baseline in mean corneal staining at all study visits (P < 0.001) in each treatment group. There was no significant between-group difference in mean corneal staining change from baseline (P = 0.107). In Cohen 2014 and Davitt 2010, the summary estimate at week six (MD -0.95, 95% CI -1.59 to -0.31; 242 participants) suggested that the PEG-containing drops were more effective than the CMC-containing drops at improving corneal staining scores (Analysis 2.3). The mean corneal fluorescein scores showed the same trend at week two. In Benelli 2010, fluorescein staining was recorded with a five-point grading scale, and results were reported as the number of participants who improved, had no change, or had worsened over the trial period. At day 30, three out of 20 participants in the PEG/PG/HP-guar group and nine out of 20 participants in the CMC group had an improved staining score (RR 3.0, 95%CI 0.95 to 9.48). In Christensen 2009, the results were reported in P value form only. Specifically, there was a significant difference in mean corneal staining score that favored the PEG/PG/HP-guar group at weeks two and six (P = 0.0009 and P = 0.01, respectively), and a mean corneal staining score that favored the same group at weeks four and six (P = 0.05 and P = 0.0009, respectively). Waduthantri 2012 reported mean and mean change from baseline corneal fluorescein staining scores at weeks one, three and six (Baylor grading scale), and they found no significant difference in corneal fluorescein staining at any study visit.

Three trials (Christensen 2004; Cohen 2014; Davitt 2010) evaluated conjunctival staining (lissamine green) at weeks one, two, four and six. The National Eye Institute grading scale was applied in Christensen 2004 and Davitt 2010. The data in Christensen 2004 and the six-week data in Cohen 2014 were insufficient to perform meta-analysis. Nevertheless, Christensen 2004 found that mean conjunctival staining scores showed significant treatment differences between groups, which favored the PEG/PG/HP-guar group at weeks two and four (P = 0.02 and P = 0.04, respectively).

Davitt 2010 found a significant between-group difference in mean conjunctival staining scores, which favored the PEG/PG/HP-guar group at week six (MD -0.80, 95% CI -1.20 to -0.40; 105 participants); Cohen 2014 did not report SDs and did not contribute to the analysis at week six, but meta-analysis of these data showed there were no significant between-group differences in mean conjunctival staining scores at the other time points tested (Analysis 2.4). With respect to the GRADE assessment, we judged this finding as low quality due to inconsistency of results and unclear risks of bias in the included trials.

Benelli 2010 evaluated tear osmolarity and best-corrected visual acuity (BCVA) after 30 days of treatment. Tear osmolarity was measured by comparing the values obtained before and five minutes after eye drop instillation. Neither test demonstrated significant between-treatment group differences.

Adverse events

Two trials (Cohen 2014; Davitt 2010) reported total adverse events, but the I^2 statistic value was 81%, which indicates that there was considerable heterogeneity and the effect estimate yields uncertainty (Analysis 2.5). Three trials (Christensen 2004; Cohen 2014; Davitt 2010) reported the number of participants who discontinued the trial due to adverse events and showed that fewer participants in the PEG/PG/HP-guar groups discontinued the trial for adverse events compared with participants in the CMC group (summary risk ratio (RR) 0.16, 95% CI 0.03 to 0.91; 339 participants) (Analysis 2.5). We downgraded the quality of the body of evidence according to the GRADE system by one level from high to moderate, because few events accounted for the wide confidence intervals seen with this outcome. In Christensen 2004, three (6.7%) out of 45 of the participants in the 0.5% CMC group discontinued the trial due to treatment-related adverse events; these events included ocular discomfort, ocular pruritus, ocular hyperemia, ocular pain, and blurred vision. Christensen 2004 did not observe any serious adverse events in either group. In Cohen 2014, 14 participants (19.2%) in the PEG/PG/HP-guar group and 22 participants in the 1% CMC group experienced one or more adverse events (RR 0.65, 95% CI 0.36 to 1.16). In the CMC group, three (4.1%) participants discontinued the trial because of adverse events. In the PEG/PG/HP-guar group, nine participants (12.3%) experienced treatment-related ocular adverse events, which included foreign body sensation, eyelid margin crusting, eye pruritus, eye allergy, and eye pain, while 15 participants (20.3%) in the 1.0% CMC group experienced treatment-related ocular adverse events, which included foreign body sensation, eyelid margin crusting, eye pain, reduced visual acuity, abnormal eye sensation, and eye irritation. This trial did not report any serious treatment-related adverse events. In Davitt 2010, 13 participants (25.0%) in the PEG/PG/HP-guar group reported 17 adverse events. Of these events, four were treatment-related adverse events (eye irritation, eyelid margin crusting, and blurred vision). In the 0.5% CMC group, six participants (11.3%) reported 11 adverse events; however, only seven of these were related to the treatment (foreign body sensation, eye irritation, blurred vision, increased lacrimation, and ocular hyperemia). Two participants who reported eye irritation in the 0.5% CMC group discontinued the trial due to the adverse events. No serious treatment-related adverse events were reported in this trial.

Waduthantri 2012 reported that no adverse events were observed in either treatment group. Christensen 2009 and Benelli 2010 did not report adverse events in their trials.

3. Polyethylene glycol (PEG) 400 plus propylene glycol (PG) or sodium hyaluronate versus hydroxypropyl methylcellulose (HPMC) carboxymethylcellulose (CMC) sodium (one trial)

In Comez 2013, each eye of a single participant was assigned to a different artificial tear. Participants were randomized to either 0.4% PEG 400 plus 0.3% PG (Systane®) in the right eye and 15% hyaluronate (Eyestil®) in the left eye, or 0.3% HPMC (Tears Naturale®) in the right eye and 0.5% CMC (Refresh® Tears) in the left eye. Analysis was performed without taking into account the non-independence of the eyes. Of the 43 moderate or severe dry eye participants who were randomized, 13 (30.2%) were lost to follow-up during the first three months of the trial, and were not included in the analysis.

Primary outcomes

The OSDI questionnaire was used to assess the patient-reported dry eye symptoms at baseline and at 2, 4, and 12 weeks. We did not perform any meta-analysis because the data were presented without taking into account the non-independence of eyes. The authors reported that both the PEG/PG (right eye) and sodium hyaluronate (left eye) group and the HPMC (right eye) and CMC (left eye) group demonstrated a significant reduction from baseline in mean OSDI scores ($P < 0.001$); however, there were no significant between-group differences.

Secondary outcomes

Schirmer's test, TBUT, and tear osmolarity were evaluated at each study visit. There were significant improvements compared to baseline at all visits in all groups for these outcomes ($P < 0.001$); however, they reported no significant between-treatment groups differences at any visit.

Adverse events

This trial found no adverse events.

4. 0.4% polyethylene glycol (PEG) 400 plus 0.3% propylene glycol (PG) versus 0.25% polyethylene glycol (PEG) 400 (one trial)

In a randomized cross-over trial, Huth 2008 compared eye drops containing 0.4% PEG 400 and 0.3% propylene glycol (PG) (Systane® Lubricant Eye Drops) versus eye drops containing 0.25% polyethylene glycol (PEG) 400 (Blink® Tears Lubricant Eye Drops). This trial was only published in abstract form.

Primary outcomes

This trial did not assess patient-reported dry eye symptoms.

Secondary outcomes

This trial did not assess any of the objective physical or diagnostic tests included in this review.

Adverse events

The author reported that no adverse events occurred in this trial.

5. 0.25% polyethylene glycol (PEG) 400 versus 1% carboxymethylcellulose (CMC) sodium (one trial)

Dumbleton 2009 compared an ophthalmic gel containing 0.25% polyethylene glycol (PEG) 400 with another ophthalmic gel containing 1% carboxymethylcellulose (CMC) sodium. Six (5.5%) out of 110 participants who were randomized discontinued during the 30-day treatment period, and were not included in the analysis. Participants in this trial were allowed to use eye drops as needed, but the number of habitual eye drops used at baseline was significantly greater in the CMC group compared with the PEG 400 group.

Primary outcomes

Changes in subjective symptoms were assessed at one, two, and four weeks with the OSDI, a study-specific ocular symptoms questionnaire (SQ), and analog scales. The OSDI questionnaire, which consists of 12 questions related to visual function, ocular symptoms, and environmental factors, showed significant improvement in dry eye symptoms at all follow-up visits ($P < 0.001$); there was also a significant difference between groups that favored the 0.25% PEG 400 group at week four ($P = 0.01$), but not at weeks one and two. The SQ assessed the frequency of symptoms (dryness, grittiness, burning, redness, lash crusting, and eyes stuck shut), based upon the previous three days. Participants in the PEG 400 group reported significantly less dryness ($P = 0.04$), grittiness ($P = 0.03$), burning ($P = 0.02$), and lash crusting ($P = 0.008$) symptoms than the CMC group at week four. The analog scale reported dry eye symptoms (overall dryness, redness, grittiness, scratchiness, soreness, and burning) based upon a 0 to 100 scale. Significantly less overall dryness ($P = 0.04$), scratchiness ($P = 0.05$), soreness ($P = 0.003$), and burning ($P = 0.01$) symptoms were reported in the 0.25% PEG 400 group compared with the 1% CMC group.

Secondary outcomes

TBUT and ocular surface staining with fluorescein and lissamine green were measured at baseline and days 7 and 30. Sufficient data were not provided to support within- and between-group comparisons. Objective assessments did not show significant differences over study periods or between groups. LogMAR visual acuity showed a small but significant increase in high- ($P = 0.004$) and low-contrast charts ($P = 0.02$), but there were no significant differences between groups.

Adverse events

One participant in the CMC group discontinued the trial due to ocular headaches and a change in taste after instillation of the drops, and another participant in the CMC group reported redder eyes. One participant in the PEG 400 group discontinued the trial due to a recurrent corneal epithelial erosion, which existed prior to the start of the trial.

6. 0.25% polyethylene glycol (PEG) 400 versus 0.3% hydroxypropyl methylcellulose (HPMC) (one trial)

In a randomized cross-over trial, Garcia-Lazaro 2011 assessed the efficacy of 0.25% polyethylene glycol (PEG) 400-based eye drops and 0.3% hydroxypropyl methylcellulose (HPMC) on dry eye by analyzing the lower tear film meniscus volume. Twenty participants were randomly assigned to one of the treatments for both eyes for one month, and then switched to another treatment for an additional month; there was a one-week washout period between phases. Measurements were taken before and after each treatment period. All participants completed the trial, and the investigators used data from the right eye for analysis.

Primary outcomes

This trial did not evaluate patient-reported symptoms of dry eye.

Secondary outcomes

Garcia-Lazaro 2011 did not assess the objective signs included in this review.

Adverse events

Garcia-Lazaro 2011 did not report on adverse events.

7. Polyethylene glycol (PEG) 400 versus hydroxypropyl (HP) guar (one trial)

In a randomized cross-over trial, Kislan 2008 assessed the effect of polyethylene glycol (PEG) 400 and hydroxypropyl (HP) guar on dry eye signs and symptoms. Eighty eyes of 40 participants were treated for four weeks in each treatment period. This trial was only published in abstract form.

Primary outcomes

This trial did not provide sufficient information on how symptoms were measured or how the data were analyzed to support additional analysis. Participants in the PEG 400 group showed significantly less blurred vision symptoms than the HP guar group ($P < 0.001$).

Secondary outcomes

TBUT, corneal lissamine green staining, and visual quality were significantly better in the PEG 400 group ($P < 0.001$, P 0.01, and $P < 0.001$ respectively) than in the HP-guar group.

Adverse events

Kislan 2008 did not report on adverse events.

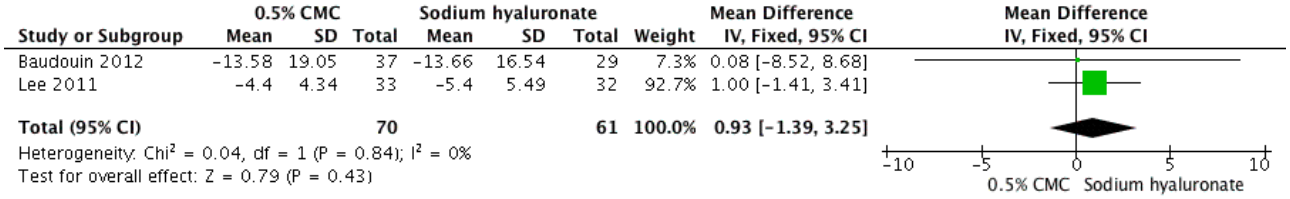
8. 0.5% carboxymethylcellulose (CMC) eye drop versus sodium hyaluronate-based eye drop (three trials)

Three trials compared 0.5% carboxymethylcellulose (CMC) with sodium hyaluronate-based eye drops for treating dry eye (Barabino 2014; Baudouin 2012; Lee 2011). Barabino 2014 included 0.2% tamarind seed polysaccharide in their 0.2% hyaluronic acid formulation. Baudouin 2012 used 0.18% sodium hyaluronate (Vismed®), and Lee 2011 used 0.1% sodium hyaluronate (Kynex). The duration of trials ranged from two (Lee 2011) to three months (Barabino 2014; Baudouin 2012). Of the 82 participants randomized in Baudouin 2012, five (6.1%) and 16 (19.5%) were not included due to exclusion or were lost to follow-up in the intention-to-treat and per-protocol analyses, respectively. All 48 of the Barabino 2014 participants who were randomized were included in their final analysis. Of the 67 mild-to-moderate dry eye participants who were randomized (34 in the sodium hyaluronate group and 33 in the CMC group) in Lee 2011, two participants in the sodium hyaluronate group were lost to follow-up and not included in their analysis.

Primary outcomes

Two trials assessed subjective symptoms by using the OSDI (Barabino 2014; Baudouin 2012), and one trial (Lee 2011) assessed seven patient-reported dry eye symptoms (burning, foreign body sensation, itching, redness, pain, photophobia, and vision blurring) via severity scores (range 1 to 7) at weeks four and eight. Dry eye symptom scores showed significant improvement from baseline in both treatment groups at weeks four and eight in Lee 2011 and at month three in Baudouin 2012, but meta-analysis found uncertainty in the between-group difference (MD 0.93, 95% CI -1.39 to 3.25; 131 participants; Analysis 3.1; Figure 4). We downgraded the GRADE assessment for this outcome from high to low quality because of high risk performance bias and attrition bias in the included trials and imprecision. Barabino 2014 was not included in the meta-analysis because of insufficient data.

Figure 4. Forest plot of comparison: 3 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate, outcome: 3.1 Mean change from baseline in symptom scores at Month 1.



Secondary outcomes

Barabino 2014 and Baudouin 2012 performed Schirmer's test, but these data were insufficient for meta-analysis. Barabino 2014 reported no significant within- or between-group differences for Schirmer's test. Baudouin 2012 reported significant between-group differences for mean change from baseline for Schirmer's test at day 35.

Barabino 2014, Baudouin 2012 and Lee 2011 analyzed TBUT, but only two of these trials (Baudouin 2012; Lee 2011) provided sufficient data for meta-analysis. Specifically, Baudouin 2012 and Lee 2011 found that both the CMC and sodium hyaluronate groups had improved TBUTs, but with no significant between-group differences in mean change in TBUT at one month (Analysis 3.2). We classified the quality of the body of evidence as moderate for this outcome due to high risk of bias in the included trials.

Baudouin 2012 reported total ocular staining scores (range 0 to 15) at day 35 and month three. Scores were derived from the sum corneal fluorescein staining score and the nasal and temporal bulbar conjunctival lissamine green staining scores (Oxford grading scale; range 0 to 5 for each region). Barabino 2014 reported total scores for corneal and conjunctival lissamine green staining (National Eye Institute grading scale; range 0 to 18) at day 84. In Lee 2011, a total corneal staining scores in five regions of the cornea (central, superior, temporal, nasal, and inferior; range 0 to 3 in each region), and a total conjunctival staining score in six areas of the conjunctiva (three portions of the temporal conjunctiva and three portions of the nasal conjunctiva; range 0 to 3 in each area) were reported at weeks four and eight.

At month one, total corneal staining scores improved in both groups in two trials, but without significant differences between groups (MD -0.14, 95% CI -0.53 to 0.24; 131 participants; Analysis 3.3). At month three, mean total ocular staining scores improved in both groups in both trials, but the difference between treatment groups was not significant (MD 0.46, 95% CI -0.48 to 1.40; 110 participants; Analysis 3.4). We downgraded by two levels on GRADE assessment from high to low for this outcome due to high risk of bias in the included trials and high heterogeneity across trials.

Adverse events

In Baudouin 2012, three participants (7.3%) in the CMC group reported keratitis, conjunctival hemorrhage, hypersensitivity, and upper limb fracture, and six participants (15.8%) in the hyaluronic acid group reported eye disorders including keratitis, conjunctival hyperemia, viral conjunctivitis, instillation site pain, amyotrophic lateral sclerosis, and erythema. Barabino 2014 did not report adverse events, and Lee 2011 did not observe any adverse events during their trial.

9. 0.5% carboxymethylcellulose (CMC) versus 0.3% hydroxypropyl methylcellulose (HPMC) (three trials)

One three-arm trial (Donshik 1998 Trial 2), one two-arm trial (Donshik 1998 Trial 3), and one four-arm trial (Simmons 2004a) compared 0.5% carboxymethylcellulose (CMC) with 0.3% hydroxypropyl methylcellulose (HPMC) artificial tears (BION Tears®). Donshik 1998 Trial 2 included 0.2% polyethylene glycol (PEG) 400 in one arm, and Simmons 2004a included 0.2% carbomer 980 ophthalmic gel and 0.3% HPMC eye drop in their other two arms. All trials had a 12-week follow-up period. Donshik 1998 Trial 2 and Donshik 1998 Trial 3 enrolled 41 and 124 participants respectively, but they did not report the numbers of participants randomized, excluded or lost to follow-up and analyzed. Donshik 1998 Trial 2 and Donshik 1998 Trial 3 had identical inclusion and exclusion criteria; they also used the worst eye for their analysis. In Simmons 2004a (published in abstract form only), 73 participants were analyzed, but they did not report the number of participants in each group.

Primary outcomes

None of the trials provided sufficient data on subjective symptoms to support meta-analysis. Donshik 1998 Trial 2 and Donshik 1998 Trial 3 analyzed 11 patient-reported dry eye symptoms, which were evaluated with a 10-point grading scale at weeks 3, 6, 9, and 12; however, they only reported the results of four symptoms (dryness, itching, tearing, and foreign body sensation) at baseline and at 12 weeks. In Donshik 1998 Trial 2, the authors reported that the HPMC group showed a non-significant improvement in dryness, itching, and foreign body sensation symptoms at 12 weeks. In Donshik 1998 Trial 3, they found significant improvements in all four reported symptoms after 12 weeks in the CMC-based artificial tear group,

and significant improvements in all symptoms except tearing in the HPMC group. Simmons 2004a did not evaluate subjective symptoms.

Secondary outcomes

Donshik 1998 Trial 2 and Donshik 1998 Trial 3 reported rose bengal staining score at baseline and at the end of follow-up; neither trial provided sufficient data for meta-analysis. In Donshik 1998 Trial 3, the mean change in rose bengal staining scores from baseline at week six was significant (P < 0.001) in both treatment groups, while Donshik 1998 Trial 2 did not observe any significant improvements in any group tested. Simmons 2004a did not perform an objective physical examination or any diagnostic tests.

Adverse events

None of the trials reported adverse events.

10. 0.5% carboxymethylcellulose (CMC) sodium versus 1% carboxymethylcellulose (CMC) sodium (one trial)

In a six-week trial, Simmons 2007 compared 0.5% carboxymethylcellulose (CMC) sodium (Refresh Tears®) and 1% CMC sodium (Refresh Liquigel®). One hundred and three participants were enrolled, and 99 of them (96.1%) completed the trial. There was a two-week run-in period with 0.2% hydroxypropyl methylcellulose (HPMC) (Visine® Tears®) before the 30-day study treatment began.

Primary outcomes

The sum frequency of 15 patient-reported symptoms (each graded on a 0 to 4 scale) was divided by four times the number of questions answered (a possible range of 0 (no symptom) to 1 (constant symptoms)) to determine the participant's subjective symptoms. There were insufficient data to perform within- or between-group comparisons. The reductions of symptoms from baseline was significant at day seven in both treatment groups (P < 0.001 in the 0.5% CMC group and P = 0.005 in the 1% CMC group), but the differences in reduction at day 30 from baseline was not significantly different between groups.

Secondary outcomes

Corneal and interpalpebral conjunctival staining with fluorescein was measured by using a modified Oxford grading scale. Numerical data were not available to allow us to perform within- or between-group comparisons. The authors reported a significant reductions in staining scores from baseline at days seven and 30 (P < 0.001), and this reduction was significantly greater in the 1% CMC group than in the 0.5% CMC group at day 30 (P = 0.01). Visual acuity changed by two or more lines in one participant in the 1% CMC group, and no visual acuity changes were found in the 0.5% CMC group.

Adverse events

There were more adverse events reported by participants in the 1% CMC group than in the 0.5% CMC group. Visual disturbance due to transient blurring was reported among 22.6% of participants in the 1% CMC group and 4.0% in the 0.5% CMC group. Eye discharge due to crusty, matted, or sticky eyes was reported in 13.2% and 2.0% of participants in the 1.0% and the 0.5% CMC groups respectively.

11. Lipid-based versus aqueous eye drops containing carboxymethylcellulose (CMC) (one trial)

In 30-day randomized controlled trial, Simmons 2015a compared four formulations containing carboxymethylcellulose (CMC): a preservative-free lipid tear formulation (LT UD group, Refresh Optive® Advanced Sensitive, unit-dose), a preservative-free aqueous tear formulation (AqT UD group, Refresh Optive® Sensitive, unit-dose), preserved multidose lipid tear formulation (LT MD group, Refresh Optive® Advanced Multidose), and preserved multidose aqueous tear formulation (AqT MD group, Refresh Optive® Multidose). Of 315 participants randomized, 310 (98.4%) completed the trial, and all randomized participants were included in ITT analysis. Participants were allowed to use the assigned treatment in both eyes as needed at least twice daily, and the median frequency of instillation was three times per day in each group.

Primary outcomes

Subjective symptoms of dry eye were assessed by using OSDI score at each follow-up visit of days 7 and 30. There were insufficient data to perform between-group comparisons. The authors reported that the mean change from baseline in OSDI score showed statistically significant improvements at days 7 and 30 in each intervention group (P < 0.001).

Secondary outcomes

TBUT, Schirmer's test, corneal staining with fluorescein, and conjunctival staining with lissamine green were measured at each follow-up visit. Significant improvements from baseline were reported at both days 7 and 30 in TBUT (P < 0.05) and Schirmer's test (P < 0.05) for all groups, but there were no between-group differences in mean changes in those assessments. Ocular staining was evaluated by using the modified National Eye Institute grid (range from 0 to 5). Corneal staining showed significant improvements from baseline at each study visit for all treatment groups (P < 0.05), except the LT MD group. The mean change at day 30 was significantly greater in the AqT UD group compared with that in the LT UD group (MD 0.78; P = 0.045), and in AqT MD group compared with LT MD group (MD 1.5; P = 0.004). Conjunctival staining also demonstrated significant reduction from baseline at days 7 and 30 in the AqT UD group (P < 0.001) and at day 7 in the AqT MD group (P < 0.05), but not in the lipid tear formulation groups. The trial authors reported that no statistically and clinically relevant between-group differences were observed for this outcome.

Adverse events

Treatment-emergent adverse events were reported in 12 (11.4%) participants in the LT UD group, 16 (15.5%) in the AqT UD group, 7 (13.7%) in the LT MD group, and 6 (10.7%) in the AqT MD group. Three participants (one each in the LT UD, LT MD, and AqT MD group) discontinued the study due to adverse events. The most frequent adverse events were instillation site pain and blurred vision, which were reported from 2.9% to 3.9% of participants in each group.

12. Two different concentrations of carboxymethylcellulose (CMC) plus hyaluronic acid versus another CMC (one trial)

Simmons 2015b compared three carboxymethylcellulose (CMC)-based artificial tear drops. Two were investigational artificial tears containing different concentrations of CMC and hyaluronic acid

(CHO-1, Optive Fusion and CHO-2), and another CMC artificial tear (Refresh Tears) was used as an active control. Participants were instructed to use the assigned treatment in each eye as needed at least twice daily, and the median of instillation was three times daily. Of 305 randomized participants, 286 (93.8%) completed the 3-month trial. All 305 randomized participants were included in ITT analysis.

Primary outcomes

OSDI score were used to evaluate patient-reported dry eye symptoms at days 7, 30, 60, and 90. OSDI score showed significant improvements from baseline for all follow-up visits in all treatment groups ($P < 0.05$), but there were no significant between-group differences in mean change in OSDI score at the end of trial (MD -0.22; 95% CI -4.85 to 4.41 between CHO-1 and Refresh Tears groups, and MD 1.74; 95% CI -2.89 to 6.37 between CHO-2 and Refresh Tears groups). In addition to OSDI score, four dry eye symptoms (burning/stinging, grittiness/foreign body sensation, dryness, and eye ache/pain) were assessed by using a visual analog scale. Significant improvements were observed at each study visit in each group for all symptoms ($P < 0.05$), except eye ache/pain at day 7 in the CHO-2 group. There was a significant between-group difference reported in mean improvements for dryness at day 90 in favor of CHO-1 group over CHO-2 group (MD -7.8; $P = 0.044$).

Secondary outcomes

TBUT, Schirmer's test, corneal staining, and conjunctival staining were tested at each follow-up visit. TBUT showed significant improvement from baseline at all follow-up visits in all treatment groups ($P < 0.001$) without any significant between-group differences. The mean Schirmer's test scores improved significantly at day 7 in the CHO-1 group, and days 7 and 90 in the CHO-2 groups ($P < 0.05$), and the increases were significantly greater in the CHO-2 group compared with the Refresh Tears group at day 7 (MD 1.6 mm/5min; $P = 0.023$). Corneal and conjunctival staining were evaluated by using a modified National Eye Institute scale. The authors reported that there was a significant differences in the mean change in corneal staining score from baseline that favored the CHO-1 group over the Refresh Tears group at day 7 (MD: -0.9; $P = 0.036$), and day 90 (MD -1.1; $P = 0.015$).

Adverse events

Treatment-related adverse events were reported in 3.9% of the participants in the CHO-1 group, 7.9% of the participatns in the CHO-2 group, and 5.8% of the participants in the Refresh Tears group. 3.0% of the participants in the CHO-2 group and 2.9% of the participants in the Refresh Tears group discontinued the study due to adverse events. The most common adverse event was eye irritation, which were reported in nine participants (5% in the CHO group and 3.9% in the Refresh Tears group). Distance visual acuity was tested as a safety outcome, and it was reported to be similar to baseline scores (no between-group differences).

13. 0.5% carboxymethylcellulose (CMC) versus 0.5% CMC plus castor oil versus 1.0% glycerine plus castor oil (one trial)

In a three-arm cross-over trial, Tomlinson 2013 compared 0.5% CMC (Refresh Tears®), 0.5% CMC plus castor oil (Optive Plus™), and 1.0% glycerine plus castor oil (Refresh Ultra®). Of the 19 dry-eye participants randomized, one participant was lost to follow-up, and the remaining 18 completed three two-week treatments. There was a minimum of a one-week washout period between each treatment phase.

Primary outcomes

The trial assessed patient-reported dry eye symptoms before and after each two-week treatment phase with the OSDI questionnaire. OSDI scores showed significant improvement after two weeks in all groups tested ($P = 0.001$). There were insufficient data for between-group comparisons.

Secondary outcomes

TBUT and tear osmolarity were evaluated before and after the treatment periods. Sufficient data for calculating between-group differences were unavailable for any outcome. There were significant improvements in both TBUT ($P < 0.01$) and tear osmolarity values ($P < 0.01$).

Adverse events

Tomlinson 2013 did not report adverse events.

14. 1.0% carboxymethylcellulose (CMC) versus 0.18% sodium hyaluronate (one trial)

Brignole 2005 compared 1% carboxymethylcellulose (CMC) with 0.18% sodium hyaluronate (Vismed) to treat dry eye syndrome with superficial keratitis. Twenty-two participants (11 per group) were randomized and all but one participant in the sodium hyaluronate group completed the 56-day trial.

Primary outcomes

The trial assessed patient-reported subjective dry eye symptoms with a 0 to 100 mm visual analog scale by summing five symptom scores (soreness, scratchiness, dryness, grittiness, and burning) to calculate a total score at days 7, 28 and 56. The authors reported that there was a trend toward faster improvement in the sodium hyaluronate group than in the CMC group, although 90% of participants in both groups showed a reduction in total symptom scores at day 56. In terms of each symptom, comfort scores were higher in the sodium hyaluronate group compared with the CMC group at each visit; this difference was significant at day seven ($P = 0.039$).

Secondary outcomes

TBUT, fluorescein staining scores, and lissamine green staining scores were reported at 7, 28 and 56 days after treatment. There were nonsignificant improvements from baseline at each visit in ocular staining scores, but there were no significant differences between treatment groups. TBUT slightly improved in both groups, but without significant differences between groups at any visit.

Adverse events

No adverse events were observed in this trial.

15. 1.0% carboxymethylcellulose (CMC) versus 0.3% hydroxypropyl methylcellulose (HPMC) (two trials)

Two trials (Boisjoly 2003; Grene 1992) compared 1.0% carboxymethylcellulose (CMC) with 0.3% hydroxypropyl

methylcellulose (HPMC); however, Boisjoly 2003 analyzed ophthalmic gels and Grene 1992 analyzed ophthalmic solutions. Boisjoly 2003 performed a randomized, cross-over trial with a two-week washout period between the two treatment periods, while Grene 1992 performed a randomized, parallel-group trial. Given these differences, and the fact that Boisjoly 2003 did not separately report data from the two segments of their trial, we could not conduct a meta-analysis with these data.

Primary outcomes

Grene 1992 assessed five patient-reported symptoms (burning/stinging, itching, foreign body sensation, dryness, and photophobia) by using a four-point grading scale; they then summed those symptoms at four and eight weeks. These data were insufficient for meta-analysis, since the number of participants in each group was not reported. The sum of symptoms score significantly improved at weeks four and eight compared to baseline in the 1.0% CMC group (MD -1.6, standard deviation (SD) 2.71; P = 0.004 at week four; MD -2.0, SD 2.58; P = 0.001 at week eight), but not in the 0.3% HPMC group. The improvement in the sum of symptoms between groups was reported to significantly favor the 1.0% CMC group over the 0.3% HPMC group (MD -1.6, P = 0.03 at week four; MD -2.0, P = 0.009 at week eight) at both four and eight weeks.

Boisjoly 2003 analyzed seven subjective symptoms (stinging or burning, itching, sandiness or grittiness, blurred vision, dryness, light sensitivity, and pain or soreness) at four weeks after each treatment with a five-point grading scale. The combined data from the two treatment periods were reported regardless of the order in which the data were received. There were insufficient data to perform paired analysis. Boisjoly 2003 reported significant improvements after four weeks of treatment compared with baseline in five symptoms (stinging or burning, itching, sandiness/grittiness, light sensitivity, and pain or soreness) for both treatments. The authors also reported that dryness symptoms significantly improved during the 0.3% HPMC treatment period, but found no improvements during the 1.0% CMC treatment period.

Secondary outcomes

Neither trial provided sufficient data to conduct a meta-analysis of secondary outcomes. Grene 1992 analyzed Schirmer's test and ocular fluorescein staining at five locations (superior conjunctiva, nasal conjunctiva, inferior conjunctiva, temporal conjunctiva, and cornea) with a five-point grading scale. Grene 1992 did not find any between-group differences or any change from baseline differences at eight weeks for either treatment for Schirmer's test. Conversely, Grene 1992 found that sum fluorescein staining scores did significantly decrease at weeks one, four and eight in the 1.0% CMC group (MD -1.3, SD 1.64; P < 0.001 at week eight), but the 0.3% HPMC group only had a significant decrease at week one (numerical data not provided). The sum difference in ocular fluorescein staining between groups significantly favored the 1.0% CMC group at weeks four and eight (P = 0.02). Boisjoly 2003 did not find an improvement in Schirmer's test, TBUT, interpalpebral conjunctival staining, or corneal staining in either treatment group.

Adverse events

Grene 1992 had one participant in the 1.0% CMC group who discontinued the trial due to blurring and discomfort. Boisjoly 2003 did not report any adverse events.

16. 1% carboxymethylcellulose (CMC) versus 0.4% carbomer-based gel (one trial)

Xiao 2008 compared a 1% carboxymethylcellulose (CMC)-based artificial tear with a 0.4% carbomer-based gel. All 60 participants who were randomized were included in the final analysis at the end of the three-month trial. In this trial, individual participants were randomly assigned to one of the intervention groups, but each eye was separately used for analysis without taking into account the non-independence of each eye.

Primary outcomes

Four patient-reported dry eye symptoms (dryness, foreign body sensation, burning sensation, and pain) were evaluated at baseline and three months after treatment; changes were judged by the proportion of eyes that achieved "marked effective," "effective," or "ineffective" changes. Insufficient data were provided to determine unit-of-analysis errors for this trial. The authors reported that each symptom showed improvement after treatment in both intervention groups, and the carbomer gel was found to be more effective at treating each symptom than the CMC artificial tear.

Secondary outcomes

Schirmer's test, TBUT, and corneal fluorescein staining were evaluated at baseline and week three by determining if there were "marked effective," "effective," or "ineffective" changes. There were insufficient data to conduct between- and within-group analysis due to the unit-of-analysis error present in the dataset. The authors reported that the improvement in each objective assessment was significantly greater in the carbomer gel group than in the CMC group.

Adverse events

Xiao 2008 did not report adverse events.

17. 0.2% carbomer versus 0.3% hydroxypropyl methylcellulose (HPMC) versus 0.3% anhydrous liquid lanolin (one trial)

In a three-arm randomized controlled trial, Wang 2007 assessed the efficacy, safety, and local tolerance of three artificial tears containing 0.2% carbomer, 0.3% hydroxypropyl methylcellulose (HPMC), or 0.3% anhydrous liquid lanolin. Of the 80 participants who were randomized, 13 (16.3%) were excluded during the four-week study period, and were not included in the analysis.

Primary outcomes

Five subjective symptoms (foreign body sensation, burning sensation, dry eye sensation, itching, and pain) were evaluated by using a four-point grading scale at baseline, and at two and four weeks after treatments. Sufficient data were not available for group comparisons. The authors reported that total subjective symptoms showed an improvement in all three groups at weeks two and four, and there were no significant between-group differences in changes from baseline symptoms.

Secondary outcomes

Schirmer's test and TBUTs were measured at baseline, and at weeks two and four. Data were not available to perform between- and within-group analysis. Wang 2007 reported that Schirmer's test values significantly improved at weeks two and four in all three groups. The changes from baseline were significantly greater in the carbomer- and HPMC-based formulations groups than in the anhydrous liquid lanolin group (P < 0.05). TBUT results showed significant improvement at weeks two and four, and the changes from baseline were significantly greater in the carbomer-based formulation group compared with the other two groups.

Adverse events

Safety was assessed by analyzing sticky eyelids, burning sensation symptoms, and blurred vision. There was a decreased trend for burning sensation symptoms and blurred vision, and an increased trend for sticky eyelids in the 0.3% anhydrous liquid lanolin group. All three values decreased in the 0.2% carbomer and the 0.3% HPMC groups.

18. 0.2% carbomer-based lipid-containing gel versus hydroxypropyl (HP)-guar gel artificial tear (one trial)

Wang 2010 compared a 0.2% carbomer-based lipid-containing gel with a hydroxypropyl (HP)-guar gel. All 30 participants who were randomized completed the one-month trial.

Primary outcomes

Five subjective symptoms (foreign body sensation, burning sensation, dry eye sensation, itching, and pain) were assessed with a four-point grading scale at baseline, and at two and four weeks after treatment. Data were insufficient for between- and within-group analysis since the authors only reported the median and the range of each symptom reported. The authors reported symptom improvements at two weeks compared to baseline in both groups.

Secondary outcomes

Schirmer's test and TBUT were evaluated at baseline and at two and four weeks. Both tests showed improvement at two and four weeks after treatment in both intervention groups. The change in Schirmer's test values from baseline were significantly greater in the carbomer-based gel group than in the HP-guar gel group at weeks two and four.

Adverse events

Burning sensation, blurred vision, and sticky eyelids were assessed at weeks two and four. The authors reported that clinically important changes were not observed for these parameters; however, one participant in the HP-guar group experienced mild blurred vision during the trial.

19. 0.3% carbomer ophthalmic gel versus 0.18% sodium hyaluronate (two trials)

Two trials (Baeyens 2012; Johnson 2008) compared 0.3% carbomer (Lacryvisc®) with 0.18% sodium hyaluronate (Vismed®). As shown above, in the three-month trial Baeyens 2012, 97 participants in the carbomer group and 106 participants in the sodium hyaluronate group were included in the intention-to-treat analysis. The worst eye was chosen for the analysis in this trial. In Johnson 2008's one-month trial, 65 participants with moderate dry eye were randomized (33 to the carbomer group, 32 to the sodium hyaluronate group), and all participants completed the trial. Johnson 2008 randomly selected one eye for analysis.

Primary outcomes

In Baeyens 2012, the sum of frequency scores for five dry eye symptoms (soreness, scratchiness, dryness, grittiness, and burning) was calculated at days 28, 56, and 84. In Johnson 2008, patient-reported dry eye symptoms were evaluated by using the Ocular Comfort Index (OCI), which assesses the frequency and intensity of five dry eye symptoms (dryness, grittiness, stinging, pain, and itching) on a 0 to 100 unit scale. Baeyens 2012 reported mean scores and mean changes from baseline, while Johnson 2008 reported medians and 25th and 75th percentiles; these differences prevented meta-analysis. Johnson 2008 reported that both groups had significantly reduced intensity and severity of dry eye symptoms after one month of treatment (P < 0.01), but they did not find significant between-group difference (P = 0.94). Baeyens 2012 demonstrated non-inferiority of sodium hyaluronate versus carbomer for subjective symptoms at day 28.

Secondary outcomes

Baeyens 2012 evaluated Schirmer's test, TBUT, ocular staining with lissamine green (summed scores ranging from 0 to 12), and fluorescein staining (global score of type and extent ranging from 0 to 7) at each visit. There was a trend toward improvement in TBUTs that favored the 0.18% sodium hyaluronate group over the 0.3% carbomer group at each visit, but there were no significant between-group differences for any of these outcomes. Johnson 2008 assessed TBUT, noninvasive break-up time (NIBUT), corneal fluorescein staining (Oxford grading scale), and conjunctival staining with lissamine green (Oxford grading scale) after one month of treatment. Staining scores showed significant improvements in both groups at month one (P < 0.01), and these improvements were significantly greater in the participants treated with sodium hyaluronate than in the participants treated with carbomer (corneal staining, P = 0.04; conjunctival staining, P = 0.01).

Adverse events

Baeyens 2012 reported that 55.2% of the participants in the carbomer group and 50.0% in the sodium hyaluronate group experienced blurred vision at day 84. Johnson 2008 did not report adverse events.

20. Carbomer ophthalmic gels containing different preservatives (one trial)

Bron 1998a compared two carbomer 940-based ophthalmic gels containing different preservatives; one was preserved with 0.01% benzalkonium chloride (marketed as Lacrinorm or GelTears), and the other was preserved with 0.01% cetrimide (marketed as Viscotears, Vidisic, or Lacrigel). Of the 179 participants who were randomized, 160 (89.4%) completed the four-week trial, and all participants were included in the final efficacy analysis. At baseline, participants who received the ophthalmic gel that was preserved with cetrimide were significantly older (MD 6.1 years, 95% CI 1.4 to 10.8), and they had an earlier dry eye diagnosis (MD 9.8 months, 95% CI 5.7 to 44.3) than participants who received the ophthalmic gel that was preserved with benzalkonium chloride.

Primary outcomes

Bron 1998a evaluated four subjective symptoms (foreign body sensation, ocular dryness, burning or pain, and photophobia) at zero, two and four weeks (total scores ranged from 0 to 12). There were no significant total changes in scores from baseline between the intervention groups.

Secondary outcomes

Schirmer's test, TBUT, ocular fluorescein staining, and ocular lissamine green staining were tested at days 0, 15, and 30. There were insufficient numerical data reported to support between- or within-group comparisons. The results of the above outcomes did not show significant differences between the intervention groups.

Adverse events

Twenty-one (22.8%) out of 92 participants experienced 24 adverse events while using the ophthalmic gel preserved with benzalkonium chloride, and 17 (19.5%) out of 87 participants reported 33 adverse events while using the ophthalmic gel preserved with cetrimide. Of these adverse events, 14 reported by 14 participants were considered to be related to the treatment: blurred vision four (three in the benzalkonium chloride group and one in the cetrimide group), stinging four (three in the benzalkonium chloride group and one in the cetrimide group), sticky eyes two (cetrimide group), hyperemia one (benzalkonium chloride group), and one grittiness, one soreness, and one redness in the cetrimide group. Five participants in the benzalkonium chloride group and four in the cetrimide group discontinued the treatment due to adverse events.

21. 0.2% polyacrylic acid (PAA) versus 1.4% polyvinyl alcohol (PVA) (three trials)

0.2% polyacrylic acid (PAA) (Visco tears®) and 1.4% polyvinyl alcohol (PVA) were compared in three trials (Brodwall 1997; Bron 1998b; Foley-Nolan 1995). Follow-up periods ranged from four to six weeks, and 79/85 participants (92.9%) in Brodwall 1997, 80/90 (88.9%) in Bron 1998b, and 80/91 (87.9%) in Foley-Nolan 1995 completed their trials. Brodwall 1997 and Bron 1998b allowed participants to use drops as needed during their treatment, and they used the participant's worst eye in their analyses. Foley-Nolan 1995 was only published in abstract form.

Primary outcomes

Brodwall 1997 and Bron 1998b analyzed five patient-reported dry eye symptoms (foreign body sensation or gritty sensation, burning sensation, dry eye sensation, photophobia, and others) with a four-point grading scale at baseline and at two and four weeks, and at baseline and at three and six weeks, respectively. Neither Brodwall 1997 nor Bron 1998b provided sufficient data for meta-analysis. Brodwall 1997 reported significant improvement from baseline at week four in the 0.2% PAA group compared with the 1.4% PVA for foreign body sensation (P = 0.02), burning sensation (P = 0.02), and dry eye sensation (P = 0.01). Bron 1998b observed significant between-group differences that favored the 0.2% PAA group (dry eye sensation (P = 0.009) at week three, and photophobia (P = 0.04) and dry eye sensation (P = 0.01) at week six).

Secondary outcomes

Brodwall 1997 and Bron 1998b measured TBUT at each study visit, but there were insufficient data to perform meta-analysis. Brodwall 1997 reported no significant differences in TBUT between and within groups at weeks two and four. In Bron 1998b, TBUT values significantly increased at three and six weeks in both groups (P < 0.0001), and these increases were significantly greater in the 0.2% PAA group than in the 1.4% PVA group at three weeks (MD 0.8, 95% CI 0.2 to 1.4) and at six weeks (MD 1.0, 95% CI 0.4 to 1.6). Brodwall 1997 and Bron 1998b also performed Schirmer's test before and after the treatments, but again there were insufficient data to perform meta-analysis. Brodwall 1997 reported that there were no significant within- or between-group differences for Schirmer's test. In Bron 1998b, Schimer's test values significantly increased at week six in both treatment groups (P = 0.0001), but with no between-groups difference (MD 1.0, 95% CI -0.4 to 2.4).

Adverse events

Brodwall 1997 had one participant in the 0.2% PAA group who experienced poor tolerance and sticky eyelids, and who discontinued treatment. They also had one participant in the 1.4% PVA group who reported a mild ocular hypersensitivity reaction. Bron 1998b reported two treatment-related adverse events (poor tolerance and mild ocular hypersensitivity) in the 0.2% PAA group; one participant discontinued treatment due to poor tolerance. Foley-Nolan 1995 reported that there were two non-serious treatment-related adverse events in the 0.2% PAA group.

22. 1.4% polyvinyl alcohol (PVA) versus 0.1% sodium hyaluronate (one trial)

Nelson 1988 compared 1.4% polyvinyl alcohol (PVA) with 0.1% sodium hyaluronate at baseline and at one, four and eight weeks. Of the 36 participants randomized, one participant in the PVA group withdrew due to dissatisfaction with the treatment; the remaining 35 participants (97.2%) completed the eight-week trial.

Primary outcomes

Pain or discomfort was evaluated by using a visual analog scale that ranged from 1 to 100. There were significant changes in mean score from baseline in both groups at each study visit (P < 0.05), but there were no significant differences between groups.

Secondary outcomes

Rose bengal staining, Schirmer's test, TBUT, and tear film osmolalities were evaluated at each study visit. The mean percentage of change from baseline was significant (P < 0.05) at weeks one and four in the sodium hyaluronate group and at weeks four and eight in the PVA group for rose bengal staining, at week one in the PVA group for Schimer's test, at all study visit in the sodium hyaluronate group for TBUT, and at week eight for the sodium hyaluronate group for tear film osmolalities. There were no significant between-group differences in any diagnostic test at any study visit.

Adverse events

No adverse events were observed in this trial.

23. 1.4% polyvinyl alcohol (PVA) versus carbomer-based ophthalmic gel (one trial)

Marner 1996 compared 1.4% polyvinyl alcohol (PVA)-based artificial tears and a carbomer-containing viscous gel in a cross-over trial. Of the 61 participants randomized, six (9.8%) were excluded from the efficacy analysis. In this cross-over trial, there was no washout period between the two treatment periods. The authors reported that their estimated treatment effects were not influenced by carry-over effects or period effects.

Primary outcomes

A four-point grading scale was used for dryness, burning, foreign body sensation, photophobia, pain, difficulty in opening eyes, and other symptoms, to assess patient-reported symptoms at the end of each two-week treatment phase; they also reported the sum of these symptoms scores (range 0 to 21). The difference between groups significantly favored the carbomer gel for dryness (MD -0.30; P = 0.01) and sum score (MD -0.76; P = 0.04).

Secondary outcomes

Marner 1996 assessed Schirmer's test, TBUT, and rose bengal staining with the Bijsterveld grading scale (range 0 to 9 for each eye). TBUT showed significant between-treatment differences at week two that favored the carbomer gel over the PVA-based artificial tear (MD 0.78, 95% CI 0.09 to 1.46). There were no significant between-treatment differences for Schirmer's test or for rose bengal staining.

Adverse events

Twenty-three participants (38%) reported at least one adverse event during the carbomer gel treatment period, compared with five participants (8%) during the PVA-based artificial tear treatment period. Of these participants, four in the carbomer treatment period and one in the PVA treatment period discontinued the trial due to adverse events. The most common adverse event reported was blurred vision, which occurred in 22 participants during the carbomer treatment period and in one participant during the PVA treatment period.

24. 0.3% hydroxypropyl methylcellulose (HPMC) versus 0.4% hyaluronic acid (one trial)

Iester 2000 compared 0.3% hydroxypropyl methylcellulose (HPMC) with 0.4% hyaluronic acid in participants with keratoconjunctivitis sicca. Of the 135 participants randomized, 113 (83.7%) of them (55 in the HPMC group and 58 in the hyaluronic acid group) completed the trial. Follow-up examinations were performed at 15, 30 and 60 or 90 days.

Primary outcomes

Four patient-reported dry eye symptoms (burning, photophobia, foreign body sensation, and pain) were evaluated at each follow-up visit by using a five-point grading scale (0 (absent) to 4 (severe)). There was a significant decrease from baseline in all four symptoms at day 60. There were also significant differences between groups in decrease from baseline for burning (P < 0.0001 at days 15, 30, and 60), foreign body sensation (P < 0.0001 at days 15, 30, and 60), photophobia (P < 0.05 at day 15, P < 0.01 at day 30, and P < 0.0001 at day 60), and pain (P < 0.05 at day 15 and 60, and P < 0.0001 at day 30) that favored hyaluronic acid.

Secondary outcomes

Fluorescein staining, rose bengal staining, Schirmer's test, TBUT, and tear film osmolarity were assessed at each study visit. Fluorescein staining, rose bengal staining, Schirmer's test, and TBUT showed that there were significant improvements from baseline at day 60 in both treatment groups (P < 0.0001), and the differences significantly favored the hyaluronic acid group at all study visits (all P < 0.0001, except P < 0.01 at day 15 for TBUT). Tear film osmolarity was tested in 57 participants (50.4%). There were significant improvements from baseline in both groups at day 60 (P < 0.001), and the improvements were significantly greater in the participants treated with hyaluronic acid than in the participants treated with HPMC at days 15, 30 and 60 (P < 0.0001).

Adverse events

Iester 2000 did not report on adverse events.

25. Two different products containing 0.3% hydroxypropyl methylcellulose (HPMC) (one trial)

One open-label cross-over trial (Lanz 2006) compared two different OTC artificial tears (GenTeal® and Tears Naturale®) containing 0.3% hydroxypropyl methylcellulose (HPMC). Thirty-seven participants with moderate-to-severe dry eye were included. This trial was only published in abstract form.

Primary outcomes

Four dry eye symptoms (tired eyes, dryness, foreign body sensation, and burning) were assessed after four weeks of treatment. This abstract did not provide sufficient information on how symptoms were measured or how the data were analyzed; however, the abstract indicated that there were no significant differences in symptoms observed between treatments.

Secondary outcomes

Total signs of dry eye, including Schirmer's test, TBUT and corneal staining, were evaluated at baseline and at the end of each treatment period. The abstract did not provide sufficient information on how measurements or analyses were performed. The changes from baseline were reported as significantly different between treatments, with differences favoring GenTeal® (P= 0.03).

Adverse events

Adverse events were not reported in this trial.

26. 0.3% hydroxypropyl methylcellulose (HPMC) eye drops with versus without bicarbonate (one trial)

Donshik 1998 Trial 1 compared a commercially available 0.3% hydroxypropyl methylcellulose-based (HPMC) artificial tear with a formulation of this same artificial tear that lacked bicarbonate. Twenty-seven participants were enrolled, and they were analyzed at baseline, and at one, four, and eight weeks. This trial did not explicitly report the numbers of participants who were randomized to each group, who were excluded or lost to follow-up, or who were analyzed.

Primary outcomes

Four subjective dry eye symptoms (ocular discomfort, foreign body sensation, dryness, and photophobia) were evaluated with a four-point grading scale, and itching was measured with a five-point

grading scale at each study visit. Data were insufficient to support between- or within-group comparisons, since only the mean scores of each symptom were reported. The authors reported that both treatments had an improvement in all symptoms except itching.

Secondary outcomes

Mean corneal staining with rose bengal was reported at baseline and eight weeks. Data were not available to support within- or between-group comparisons. The trial did not find significant changes from baseline, although they did report a clinically significant improvement that was more than one score unit better.

Adverse events

Donshik 1998 Trial 1 did not report adverse events.

27. 0.3% hydroxypropyl methylcellulose (HPMC) versus 1.25% castor oil (one trial)

Khanal 2007 compared 0.3% hydroxypropyl methylcellulose (HPMC) with 1.25% castor oil in a one-month randomized controlled trial. Fifty-three participants were randomized, and all participants completed the trial.

Primary outcomes

This trial did not evaluate patient-reported symptoms of dry eye.

Secondary outcomes

Osmolarity was measured at baseline and one month after treatment. Mean change in osmolarity from baseline showed a trend of reduction in both groups at one month; this was a non-significant reduction that was greater in the castor oil group than in the HPMC group (MD -2.0 mOsm/L; P = 0.08).

Adverse events

Three (11.1%) out of the 27 participants in the castor oil group reported blurred vision or grittiness.

28. Trehalose plus hyaluronic acid versus polyethylene glycol (PEG) plus propylene glycol (PG) plus hydroxypropyl (HP) guar (one trial)

In a randomized, open-label, cross-over trial, Pinto-Bonilla 2015 compared the novel artificial tear (Thealoz Duo®) containing trehalose and hyaluronate with PEG/PG/HP-guar (Systane®). Seventeen participants with moderate-to-severe dry eye syndrome were randomized to one of the interventions. Participants were instructed to apply the assigned artificial tear drops five times daily for seven days followed by a washout period of five days before switching to the alternate treatment for another five days. All 17 participants were included in the final analysis.

Primary outcomes

Patient-reported symptoms of dry eye were assessed by using OSDI score and the sum of symptoms score of five domains (impact on daily life, impact on daily activities, emotional impact, impact on work, and impact on ocular comfort). The authors reported that there were no significant between-group differences in mean reduction in OSDI score (MD 6.2; P = 0.22). There was a significant difference in mean reduction for the impact at work in favor of the trehalose/hyaluronate group at day 3 (MD -1.6; P = 0.004), and day 7(MD -1.7; P = 0.010), but for none of the other symptoms measured.

Secondary outcomes

TBUT, Schirmer's test, and ocular staining according to the Oxford scheme were measured to evaluate objective signs of dry eye. The trial authors reported that there were improvements in TBUT, Schirmer's test score, and ocular staining, but no significant between-group differences were observed.

Adverse events

No adverse events were reported throughout the study period.

DISCUSSION

Summary of main results

Given the large number of artificial tear formulations compared and the wide variety of outcomes considered in this systematic review, it is difficult to propose that one OTC artificial tear formulation is superior to another for the treatment of dry eye syndrome. This lack of consensus may stem from the fact that the US regulatory process for OTC agents does not promote novel mechanisms for efficacious treatments or require clinical trials for approval of OTC agents (FDA 2015). These limitations are complicated by the fact that few trials compared the same formulations (three or fewer for each comparison of identical interventions; Table 3) and there was an absence of consistent data reporting and measurement methods used by trial investigators. Based on the limited analyses that we were able to conduct in our systematic review, we found the evidence to yield uncertainty as to whether some artificial tears may be better at treating dry eye than others in terms of improving ocular symptoms, the primary outcome of this study. We found similar contradictory results when analyzing most secondary outcomes. Nevertheless, artificial tears as a whole consistently improved ocular symptoms over the course of the included trials based on within-group analyses. Three of four placebo-controlled trials consistently found that OTC artificial tears improved ocular symptoms compared with placebo (saline or vehicle). We saw a similar trend for many of the secondary outcomes considered in this review; however, these findings were less consistent. This review also found that the use of artificial tears is relatively safe, although not without adverse events. This finding fits well with this product being available OTC, with the most common adverse events being blurred vision, ocular discomfort and foreign body sensation. Overall, we found OTC artificial tears may be safe and effective at treating dry eye; however, no one product analyzed in this review stands out as a superior dry eye treatment.

Overall completeness and applicability of evidence

The trials included in this review were acquired from many sources (e.g. peer-reviewed manuscripts, conference abstracts, FDA clinical trials), and were conducted in various settings around the world. These trials also evaluated a broad range of interventions and ocular outcomes, although there was little standardization of the outcomes. This lack of standardization is likely due to the lack of FDA guidance related to clinical trials involving OTC artificial tears (FDA 2015). Thus, the applicability of the evidence gathered in this review could be considered reasonable. Nevertheless, applicability is only a major consideration once the quality of the evidence is sufficient to support quantitative statements. Unfortunately, this is

not the case with the majority of comparisons and trials included in this review. The overall completeness of the included trials was limited by factors like being short-term (Table 2), incomplete investigator masking, industry support bias, and incomplete data reporting (Figure 2). Furthermore, we identified trial registry records for 18 trials that have been completed, but for which no results have been made available. These factors among others have limited the overall completeness and applicability of the results presented in this review, and these limitations should be considered and avoided when designing future randomized clinical trials involving OTC artificial tears.

Quality of the evidence

This review was limited to RCTs, which decrease bias by preventing participants and investigators from deciding who receives a specific intervention. Randomization also helps ensure that study groups are similar at baseline. Nevertheless, the overall quality of the evidence found during this review was low. Not all trials had equivalent groups at baseline (Aguilar 2014; Benelli 2010; Bron 1998a; Bruix 2006; Dumbleton 2009; Sullivan 1997; Waduthantri 2012). Some trials did not properly control the amount of treatment administered per day (Benelli 2010; Bron 1998a; Bruix 2006; Dumbleton 2009; Johnson 2008; Sullivan 1997; Waduthantri 2012). Several trials had high rates of attrition and limited follow-up (Figure 2; Table 2). Given the small size and marginal effectiveness seen in short-term trials, it is impossible to draw strong inferences about the effectiveness of the interventions we analyzed. The quality of evidence was also limited by factors such as most trials lacking a published protocol prior to enrolling participants, absence of trial registration, randomization procedures often not being described, and the likely influence that industry has had on which trials are presented at meetings and published in the literature.

Potential biases in the review process

Review process bias was reduced in our review by searching all publicly-reported trials and by having at least two review authors determine if a publication should be included or excluded from this review. Bias was also reduced by the fact that no review author has conducted a RCT involving OTC artificial tears. One potential bias in the review process was a departure from the protocol, in which we had intended to evaluate drugs in various categories as described by the FDA. Our review compared specific ingredients and ignored these categories because of the great variations in formulations found during the literature search. The implications of this for the inferences of this review are unknown. It is also important to consider here that the primary review outcome and several other secondary outcomes were subjective measures of patient-reported outcomes rather than an objective outcome. Although it is important to include patient-reported outcomes, this subjective variability and use of different grading scales/questionnaires limit synthesis across trials.

Agreements and disagreements with other studies or reviews

Alves 2013, Calonge 2001, Doughty 2009, and Moshirfar 2014 have all produced reviews related to OTC artificial tears. None of these reviews limited their searches to RCTs, or produced and meta-analyzed results. Alves 2013 is a systematic review that only looked at the main outcomes of each included study; this review also analyzed dry eye treatments other than artificial tears. Calonge 2001 is a general non-systematic review of currently available dry eye treatments, which did not comment on the efficacy of individual artificial tear formulations. Doughty 2009 is a systematic review of studies that only used rose bengal staining to evaluate the efficacy of artificial tears. Moshirfar 2014 is a systematic review of currently-marketed artificial tears (all others were excluded); this review included short studies (e.g. 60 minutes), and commented on how artificial tear study outcomes were likely related to funding sources. In general, when analysis was possible, the tested artificial tear formulations were found to improve signs and symptoms over the course of the included studies, although much as in our review, they found no consistent between-group differences when conducting head-to-head artificial tear comparisons

AUTHORS' CONCLUSIONS

Implications for practice

This review indicates uncertainty in the comparative effectiveness of the products we evaluated for treating dry eye. In general, the literature currently indicates that most over-the-counter (OTC) artificial tears may produce similar symptomatic relief. Nevertheless, the literature does not currently offer a strong conclusion on which artificial tears to use, because there are many contradictory reports and because, to the best of our knowledge, there are few RCTs that have made head-to-head comparisons with the more recent tear lipid-containing artificial tears (e.g. Systane Balance) and other artificial tear formulations (Aguilar 2014; Simmons 2015a).

Implications for research

This review clearly indicates that additional work is needed to systematically determine if one OTC artificial tear formulation is superior to another. This review demonstrates the need for more consistency among study designs, specifically by identifying core outcomes for all dry eye research to measure, a feature that would allow much more pertinent information to be gathered and synthesized from the systematic review process. Most importantly, outcomes for dry eye research should be driven by what is important to patients, such as relief of symptoms. This review also highlights the need to consider the validity of the outcomes considered; for example, different questionnaires and scales were used among studies to assess changes in patient-reported symptoms. Issues of multiple comparisons of various formulations potentially could be mitigated by network meta-analysis methods, which utilizes direct and indirect treatment effects to determine which works best. Also, the lack of RCTs involving recent tear lipid-containing OTC artificial tear formulations calls for additional research to determine if there are advantages to using these newer formulations (Aguilar 2014; Simmons 2015a).

Finally, we identified 18 trials (2079 participants) that were registered, but for which no data were available (no results posted in the clinical trial register record and unpublished). The lack of reporting of the trial results represents a high risk of publication bias and an ethical issue in which the research that participants volunteered to contribute to cannot be used effectively. All trials should be registered and the trial results should be made available.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aguilar 2014

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 51 participants total; 25 into the Systane group; 26 into the saline group Unit of randomization (individual or eye): individual Exclusions after randomization: 2 participants in the saline group withdrew consent Losses to follow-up: none Number analyzed: 49 participants total; 25 in the Systane group; 24 in the saline group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): Y (90%) Reported subgroup analysis (Y/N): N
Participants	Country: Argentina Age (mean ± SD, range): 44 ± 19 years, range 21 to 85 years total; 46 ± 20 years, range 21 to 85 years in the Systane group; 43 ± 18 years, range 22 to 77 years in the saline group Gender: 7 men and 18 women in the Systane group; 9 men and 15 women in the saline group Inclusion criteria: 1) aged ≥ 18 year; 2) best-corrected visual acuity ≤ 0.6 logMAR in both eyes at screening; 3) no use of topical ocular drops within approximately 24 hours before screening; 4) required to meet all the following criteria for dry eye at screening: answered at least "some of the time" to the previously published symptom eligibility question "how often have your eyes felt dry enough to want to use eye drops (artificial tears)" focusing on the past 24 hours; noninvasive tear break-up time ≤ 7 seconds in 1 or both eyes; meibomian gland expression of grade 1 or higher in both eyes; and evidence of missing meibomian glands in both eyes Exclusion criteria: 1) intolerance or hypersensitivity to any component of study treatments; 2) ocular or intraocular surgery or serious ocular trauma ≤ 6 months before enrollment; 3) current punctal occlusion of any type, use of concomitant topical ocular medications; 4) use of systemic medications that may contribute to dry eye (unless on a stable regimen for ≥ 30 days before screening and throughout the study); 5) ocular or systemic infections or conditions (e.g. epithelial herpes simplex keratitis; vaccinia, varicella, or mycobacterial infection; fungal disease; iritis) that preclude safe administration of study treatment; 6) use of contact lenses within 1 week before screening and throughout the study period; 7) participation in an investigational drug or device study ≤ 30 days before screening

Aguilar 2014 *(Continued)*

	Equivalence of baseline characteristics (Y/N): N (total corneal staining score; total conjunctival staining score)
Interventions	Intervention #1: 0.6% propylene glycol, hydroxypropyl-guar, dimyristoylphosphatidylglycerol, borate, sorbitol, and mineral oil (Systane® Balance, Alcon Laboratories, Inc.) 4 times daily Intervention #2: saline Length of follow-up: 4 weeks Notes: none
Outcomes	Primary outcome(s): noninvasive TFBUT Secondary outcome(s): corneal and conjunctival staining; goblet cell density classification; meibomian gland expression; best-corrected visual acuity Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2 and 4 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Alcon Research, Ltd., sponsored this study and funded medical writing support" Conflicts of interest: "Dr Aguilar has commercial relationships with Poen Laboratories and Merck & Co., Inc. The other authors have no conflicts of interest to disclose." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported; "patients were assigned a subject number in numerical sequence and were randomized 1:1 to receive either SYSB or SAL"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported; "patients were assigned a subject number in numerical sequence and were randomized 1:1 to receive either SYSB or SAL"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants in the saline group withdrew consent after randomization, and they were not included in the analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported

Aguilar 2014 *(Continued)*

Other bias	Unclear risk	Baseline characteristics were not equivalent; this trial was funded by a pharmaceutical company

Baeyens 2012

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (45 sites) Number randomized (total and per group): 304 participants total; 106 to the sodium hyaluronate group; 101 to the saline group; 97 to the carbomer group Unit of randomization (individual or eye): individual Exclusions after randomization: 1 in the carbomer group in ITT population Losses to follow-up: none Number analyzed: 303 total in ITT population; 106 in the sodium hyaluronate group; 101 in the saline group; 96 in the carbomer group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: France and United Kingdom Age (mean ± SD, range): 59.3 ± 15.0 years, range 20 to 90 years Gender: women 85.4% Inclusion criteria: 1) men and women aged between 18 and 80 years; 2) at least a 3-month history of dry eye; 3) 2 symptoms among soreness, scratchiness, dryness, grittiness and burning occurring at least often; 4) 3 of the 4 following objective criteria: Schirmer's test of < 10 mm/5min, TBUT of < 10 seconds, total scores of corneal staining with fluorescein of at least 3/7 and lissamine green of at least 3/12 Exclusion criteria: 1) severe dry eye; 2) refractive surgery within the last 12 months or any other ocular surgery or trauma within the last 6 months prior to trial inclusion Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.18% sodium hyaluronate solution (Vismed®, Hylovis®, or Rejena®) 2 - 4 times daily Intervention #2: placebo (saline) 2 - 4 times daily Intervention #3: 0.3% carbomer (Lacyvisc®, Laboratoires Alcon) 2 - 4 times daily Length of follow-up: 3 months Notes: there was a 7-day run-in period with a saline solution
Outcomes	Primary outcome(s): symptom frequency Secondary outcome(s): symptom intensity; impact of symptoms on daily life activities, lissamine green staining; fluorescein staining; Schirmer's test; TBUT; number of instillations; global efficacy evaluation; BCVA Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 4, 8, and 12

Baeyens 2012 *(Continued)*

	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: EudraCT 2007-001708-19 Funding source(s): none Conflicts of interest: 1 of the authors was affiliated with a pharmaceutical company Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" trial; "In this study, given that a commercially available presentation of carbomer with different shape of ampoule compared to 0.18% SH and saline was used as a comparator, carbomer was repackaged under the cGMP requirements. Each monodose was relabelled in order to keep the patient blinded to the treatment received."; it was unclear if trial personnel were masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind" trial, but it was unclear if outcome assessors were masked
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis was followed, but it was defined as "The intent-to-treat (ITT) data set was defined as patients who had at least one administration of the allocated product and a value at baseline for the parameter of the primary endpoint."; it did not include all participants who were randomized; 1 participant in the carbomer group was not included in the analysis; the last observation carried forward method was used; the authors did not state the reasons why participants dropped out of the trial although they claimed that most of them dropped out due to lack of efficacy
Selective reporting (reporting bias)	Unclear risk	Protocol did not present secondary outcomes
Other bias	Unclear risk	1 author was affiliated with a pharmaceutical company

Barabino 2014

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (4 sites) Number randomized (total and per group): 48 participants total; 23 in the Xiloial group; 25 in the Optive group Unit of randomization (individual or eye): individual Exclusions after randomization: none

Barabino 2014 *(Continued)*

	Losses to follow-up: none Number analyzed: 48 participants total; 23 in the Xiloial group; 25 in the Optive group Unit of analysis (individual or eye): individual Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Italy Age (mean ± SD, range): 52.2 ± 14.9 years in the Xiloial group; 57.1 ± 17.4 years in the Optive group Gender: 9 men and 14 women in the Xiloial group; 6 men and 19 women in the Optive group Inclusion criteria: 1) at least 18 years of age; 2) moderate dry eye disease confirmed by OSDI questionnaire between 10 and 25, TBUT < 10 seconds or Schirmer I test < 5.5 mm after 5 minutes, and lissamine green staining of the ocular surface > 2 according to National Eye Institute conjunctival grading system Exclusion criteria: 1) ocular trauma, surgery, infection or inflammation within the 3 months preceding the study; 2) concomitant ocular pathologies, eyelid, eyelash, or nasolacrimal apparatus abnormalities; 3) use of drugs affecting tearing; 4) ocular therapies within the month preceding the study, except for artificial tears if followed by a washout period; 5) neurologic or dermatologic disease affecting the health of the ocular surface; 6) contact lens wear Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (Xiloial group): 0.2% hyaluronic acid plus 0.2% tamarind seed polysaccharide (Xiloial monodose, Farmigea S.p.A.) 4 times daily Intervention #2 (Optive group): 0.5% carboxymethylcellulose sodium and 0.9% glycerin (Optive monodose, Allergan) 4 times daily Length of follow-up: 3 months Notes: there was a washout period with 0.9% NaCl
Outcomes	Primary outcome(s): OSDI; TBUT; ocular protection index; Schirmer's test; corneal and conjunctival lissamine green staining; global efficacy assessment Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, and week 2, 4, 6, 8, and 12 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Supported by a grant from Farmigea SpA in favor of the academic institutions" Conflicts of interest: none Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement

Barabino 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "Both Xiloial and Optive were primarily packaged in droppers from which any identification of the product was manually removed by a pharmacist and subsequently identified only with treatment number. Both the investigator and the patient were masked to the treatment assigned according to the masked nature of the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-masked" trial; details about masking of outcome assessors were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	High risk	Adverse events were investigated, but not reported in results
Other bias	Unclear risk	This trial was funded by a pharmaceutical company

Baudouin 2012

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: multicenter (12 sites)
	Number randomized (total and per group): 82 participants; 41 to each group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: 9 total; 3 (1 adverse events;1 consent withdrawn;1 other) in the Optive group; 6 (5 consent withdrawn; 1 other) in the Vismed group
	Losses to follow-up: 3 total; 2 in the Optive group; 1 in the Vismed group
	Number analyzed: 70 participants total; 36 in the Optive group; 34 in the Vismed group
	Unit of analysis (individual or eye): individual (worst eye)
	Reported power calculation (Y/N): Y, power of 90%
	Reported subgroup analysis (Y/N): N
Participants	Country: France
	Age (mean ± SD, range): 58.1 ± 14.2 years in the Optive group; 55.4 ± 13.4 years in the Vismed group
	Gender: 5 men and 35 women in the Optive group; 3 men and 34 women in the Vismed group
	Inclusion criteria: 1) aged ≥ 18 years; 2) OSDI score ≥ 18; 3) at least 1 eye with signs of keratoconjunctivitis sicca (total ocular staining score grade ≥ 4 and ≤ 9 on the 15-point Oxford scale) and ≥ 1 objective sign of tear deficiency (Schirmer test without anesthesia ≥ 3 and ≤ 9 mm in 5 minutes, or sum of 3 TBUT tests ≤ 30s; 4) use of artificial tears for ≥ 3 months prior to inclusion and preservative-free artificial tears at least 3 times daily for at least 2 weeks immediately prior to inclusion

Baudouin 2012 *(Continued)*

	Exclusion criteria: 1) BCVA < 1/10; 2) severe dry eye with 1 of the following conditions: eyelid abnormality, corneal disorder or abnormality, ocular surface metaplasia, filamentous keratitis, or corneal neovascularization; 3) allergy or sensitivity to study medications; 4) uncontrolled systemic disease or history or active signs of ocular trauma, infection, inflammation, allergic disease, or herpes; corneal ulcers; 5) recurrent erosions; 6) uveitis; 7) pregnant, breastfeeding, planning a pregnancy, a positive urine pregnancy test result at baseline, or unwilling to use a reliable form of contraception; 8) enrollment or participation in an investigational drug or device study within the 3 months prior to study entry Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (Optive group): 0.5% carboxymethylcellulose and the osmoprotective compatible osmolytes erythritol, L-carnitine, and glycerin with sodium chlorite (Purite®) as preservative (Optive® Multi-Dose, Allergan, Inc.) 3 - 6 times daily Intervention #2 (Vismed group): 0.18% sodium hyaluronate without preservative (Vismed® Multi, Lantibio, Inc.) 3 - 6 times daily Length of follow-up: 3 months Notes: the use of any concurrent prescription or over-the-counter medication was recorded
Outcomes	Primary outcome(s): corneal staining with fluorescein; nasal and temporal bulbar conjunctival staining with lissamine green Secondary outcome(s): OSDI score; tear osmolarity (selected centers); Schirmer's test; symptoms of dryness; treatment efficacy (TBUT; total ocular surface staining; conjunctival hyperemia; study product use throughout study); acceptability questionnaire; BCVA; tolerance Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, day 35, and month 3 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: between December 2009 and September 2010 Trial registration: not reported Funding source(s): "This study was funded by Allergan Limited, Marlow, Buckinghamshire, UK. Medical writing and editorial assistance was provided by Darwin Healthcare Communications, UK. Statistical consultation and assistance was provided by Caroline Colacchio, MSc, and Edward Matthews, MSc, of Chiltern, UK. This assistance was funded by Allergan" Conflicts of interest: 2 authors were affiliated with a pharmaceutical company; 2 authors reported consulting services to pharmaceutical companies Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"investigator-masked" trial; "Consequently, patients could not be masked to the study product because of the difference in the appearance of the vials and delivery technique of each product. To ensure single masking, study products were dispensed by a third party, external to the study site, and were delivered

Baudouin 2012 *(Continued)*

		directly to the patients and not returned to the investigational site. Patient questionnaires were administered by a staff member other than the investigator. Patients were instructed not to instill the product an hour before their visit, or reveal the nature of the product to the investigator."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"investigator-masked" trial; "To ensure single masking, study products were dispensed by a third party, external to the study site, and were delivered directly to the patients and not returned to the investigational site. Patient questionnaires were administered by a staff member other than the investigator. Patients were instructed not to instill the product an hour before their visit, or reveal the nature of the product to the investigator."
Incomplete outcome data (attrition bias) All outcomes	High risk	16/82 (19.5%) in the per-protocol analysis and 5/82 (6.1%) in the intention-to-treat analysis were not included in the final analysis
Selective reporting (reporting bias)	High risk	The results at month 3 in TBUT and Schimer's test were not reported
Other bias	Unclear risk	This trial was funded by a pharmaceutical company; two authors were affiliated with a pharmaceutical company; two authors reported consulting services to pharmaceutical companies

Benelli 2010

Methods	Study design: 3-arm randomized, parallel-group, controlled trial
	Study center: single center
	Number randomized (total and per group): 60 participants total; 20 per group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: none
	Losses to follow-up: none
	Number analyzed: 60 participants total; 20 per group
	Unit of analysis (individual or eye): individual (worst eye)
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: Italy
	Age (mean ± SD, range): not reported
	Gender: not reported
	Inclusion criteria: 1) OSDI 2 value between 30 and 60 and with a Schirmer's test of < 7 mm after 5 minutes
	Exclusion criteria: 1) non-dry eye ocular pathology undergoing treatment with topical or systemic medications for other types of ocular pathologies
	Equivalence of baseline characteristics (Y/N): N (tear osmolarity; TBUT; Schirmer's test)
Interventions	Intervention #1: 0.5% carboxymethylcellulose sodium (Cellufresh®, Allergan Inc.) up to 4 times daily

Benelli 2010 *(Continued)*

	Intervention #2: 2.5% polyethylene glycol 400 and sodium hyaluronate (Blink® Intensive Tears, Abbott Medical Optics Inc.) up to 4 times daily Intervention #3: 0.18% hydroxypropyl guar, polyethylene glycol 400, and propylene glycol (Systane®, Alcon Laboratories Inc.) up to 4 times daily (personal communication) Length of follow-up: 30 days Notes: there was a washout period of 10 days for participants who were already on treatment using lubricant eye drops
Outcomes	Primary outcome(s): tear osmolarity; corneal wavefront aberrometry; TBUT; Schirmer's test, fluorescein staining; best-corrected visual acuity Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, and day 30 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "This study was funded by an unrestricted educational grant by Abbott Medical Optics." Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was funded by a pharmaceutical company; baseline characteristics were not equivalent

Boisjoly 2003

Methods	Study design: randomized, cross-over, controlled trial Study center: multicenter (2 sites) Number randomized (total and per group): 22 participants total; 10 into the GenTeal Gel first and 12 into the Refresh Liquigel first Unit of randomization (individual or eye): individual Exclusions after randomization: 1 in the GenTeal Gel phase; the reason not reported Losses to follow-up: none Number analyzed: 21 in the GenTeal Gel treatment period; 22 in the Refresh Liquigel treatment period Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Canada Age (mean ± SD, range): 61.5 ± 10.3 years total ; 61.2 ± 10.4 years in the GenTeal Gel first; 61.7 ± 10.7 years in the Refresh Liquigel first Gender: 10 women in the GenTeal Gel first; 4 men and 8 women in the Refresh Liquigel first Inclusion criteria: 1) adults; 2) either gender; 3) moderate to severe dry eye disease defined as Schirmer's test with anesthesia of ≤ 10 mm/5minutes in at least 1 eye; 4) present signs and symptoms of dry eye despite conventional management including artificial tears drops Exclusion criteria: not reported Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.3% hypromellose and 0.22% carbomer with cetrimide as preservative (GenTeal® Gel, Novartis) 4 times daily Intervention #2: 1% carboxymethylcellulose sodium with purite as preservative (Refresh Liquigel™, Allergan) 4 times daily Length of follow-up: 4 weeks in each phase; 2 weeks of washout period between the treatment periods (personal communication) Notes: participants were instructed to instill 1 drop of study gel 4 times daily in each eye with concomitant artificial tears as needed
Outcomes	Primary outcome(s): symptoms (stinging/burning; itching; sandiness/grittiness; blurred vision; dryness); Schirmer's test; TBUT; corneal and interpalpebral conjunctival staining Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y (personal communication) Measurements taken, specify intervals at which outcomes assessed: baseline, and week 4 in each phase Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported

Boisjoly 2003 *(Continued)*

Funding source(s): "The authors received private financial support pertaining to the information published in this article from Novartis Ophthalmics"

Conflicts of interest: "The authors received private financial support pertaining to the information published in this article from Novartis Ophthalmics"

Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table was used (personal communication)
Allocation concealment (selection bias)	Unclear risk	"coded bottles" were used (personal communication)
Blinding of participants and personnel (performance bias) All outcomes	High risk	"We designed a randomized, single-masked, single observer, cross-over clinical trial"; "The study personnel were not masked because although no meds name were on the bottles, the bottles were different, one was more compressible than the other." (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"subjective symptoms were graded by a trained independent observer"; "We designed a randomized, single-masked, single observer, cross-over clinical trial" (personal communication)
Incomplete outcome data (attrition bias) All outcomes	High risk	"All except one patient crossed treatment to the alternative gel for the second treatment phase"; 1/22 (4.5%) was not included in the final analysis; the reason of exclusion was not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was a cross-over design; results were not separately reported by phases; subjects were allowed to use additional artificial tears as needed; authors received private financial support from a pharmaceutical company

Brignole 2005

Methods

Study design: randomized, parallel-group, controlled trial

Study center: single center

Number randomized (total and per group): 22 participants total; 11 per group

Unit of randomization (individual or eye): individual

Exclusions after randomization: none

Losses to follow-up: 1 in the sodium hyaluronate group

Number analyzed: 21 participants total; 10 in the sodium hyaluronate group; 11 in the CMC group

Unit of analysis (individual or eye): not reported

Reported power calculation (Y/N): N

Reported subgroup analysis (Y/N): N

Brignole 2005 *(Continued)*

Participants	Country: France Age (mean ± SD, range): 57 ± 21 years in the sodium hyaluronate group; 69 ± 21 years in the CMC group Gender: 1 man and 9 women in the sodium hyaluronate group; 11 women in the CMC group Inclusion criteria: 1) men and women; 2) 18 years of age and older; 3) documented moderate dry eye due to SS or diagnosed as primary dry eye syndrome; 4) at least 1 of the dry eye symptoms (among soreness, scratchiness, dryness, grittiness and burning), occurring at least sometimes; 5) Schirmer's test of < 10 mm wetting/5 min; 6) BUT of less than 10 secs; 7) corneal staining with fluorescein with a total score (type + extent + depth) of 3 or more; 8) women with a reliable method of contraception or who were postmenopausal Exclusion criteria: 1) severe dry eye syndrome (i.e. corneal staining with fluorescein with a depth score of 3 or more and/or severe conjunctival hyperemia and/or severe blepharitis) ; 2) ocular surgery (whatever type) or ocular trauma within the last 4 months before inclusion; 3) a current history of disease that could interfere with the assessments in this study (e.g. glaucoma) Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.18% sodium hyaluronate (Vismed, TRB CHemedica AG) 3 times daily Intervention #2: 1% carboxymethyl cellulose(Celluvisc, Allergen AG) Length of follow-up: 56 days Notes: there was a 48-hour washout without treatment before the baseline visit; no other in-eye solutions were permitted from the day 0 visit until the day 56 visit; all participants were asked not to change their dose for the whole trial if the participants took systemic medications
Outcomes	Primary outcome(s): corneal fluorescein staining; lissamine green staining; TBUT; corneal topography; tear prism height; subjective symptoms of dry eye; comfort of the eye drops Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, days 7, 28 and 56 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Brignole 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"masked-observer" trial; "Both products were supplied in their original sterile, single-use monodose container without any preservative"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"masked-observer" trial, but details about masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	One participant in the sodium hyaluronate group was lost to follow-up, and he/she was not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Brodwall 1997

Methods	Study design: randomized, parallel-group, controlled trial Study center: not reported Number randomized (total and per group): 85 participants total; 42 into the PVA group and 43 into the PAA group Unit of randomization (individual or eye): individual Exclusions after randomization: 2 participants total; 1 participant each due to drop intolerance Losses to follow-up: 4 participants total; 1 in the PVA group; 3 in the PAA group Number analyzed: 79 participants total; 41 in the PVA group; 38 in the PAA group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: not reported Age (mean ± SD, range): 61.8 in the PVA group; 60.2 in the PAA group Gender: 4 men and 38 women in the PVA group; 6 men and 37 women in the PAA group Inclusion criteria: 1) at least 2 of the following symptoms in both eyes: (a) gritty/foreign body sensation; (b) burning sensation; (c) dry eye sensation; (d) photophobia; 2) at least 1 of the following signs in both eyes: (a) Schirmer's test of < 8mm/5min on the day of recruitment; (b) tear break-up time of < 10 seconds Exclusion criteria: 1) age less than 18 years or more than 75 years; 2) pregnancy or lactation; 3) known hypersensitivity to polyacrylic acid, cetrimide, polyvinyl alcohol, benzalkonium chloride; 4) systemic therapy which may induce corneal deposits or influence lacrimal secretion; 5) naso-lacrimal obstruction; 6) external eye disease including conjunctival inflammation and/or infection and corneal scars, dystrophies and infections, intraocular inflammation; 7) wearing of contact lens; 8) any local treatment with eye drops/ointment other than for dry eye; 9) therapy-resistant dry eye; 10) noncompliance with protocol; 11) participating in another trial

Brodwall 1997 *(Continued)*

	Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (PAA group): 0.2% polyacrylic acid with 0.01% cetrimide as preservative (Visco tears®) Intervention #2 (PVA group): 1.4% polyvinyl alcohol with 0.01% benzalkonium chloride as preservative Length of follow-up: 4 weeks Notes: there was a washout period of 7 days with sodium chloride 0.9% for participants who were already on treatment on dry eye; participants were allowed to use drops as needed
Outcomes	Primary outcome(s): symptoms (foreign body sensation/gritty sensation; burning sensation; dry eye sensation; photophobia); conjunctival injection; ciliary injection; corneal and conjunctival staining; TBUT; Schirmer's test; local tolerance Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2 and 4 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: 1 author was affiliated with a pharmaceutical company Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"We therefore performed a prospective, randomised, investigator-masked, parallel-group study", but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"We therefore performed a prospective, randomised, investigator-masked, parallel-group study", but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	5/80 (6.3%) at 2 weeks and 6/85 (7.1%) at 4 weeks were not included in the final analysis; 1 participant in each group discontinued trial due to drop intolerance; 1 in the PVA group, and 3 in the PAA group were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol was not available

Brodwall 1997 *(Continued)*

Other bias	Unclear risk	The participants were allowed to use drops as needed; only the current drop users had a washout period; 1 author was affiliated with a pharmaceutical company

Bron 1998a

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (16 sites) Number randomized (total and per group): 179 participants total; 92 into the Lacrinorm group; 87 into the control group Unit of randomization (individual or eye): individual Exclusions after randomization: 19 in total; 10 in the Lacrinorm group (5 consent withdrawn; 4 adverse events; 1 adverse event and worsening of the disease); 9 in the control group (4 consent withdrawn; 4 adverse event; 1 protocol violation) Losses to follow-up: 1 in the control group Number analyzed: 179 participants total (at baseline); 92 in the Lacrinorm group (at baseline); 87 in the control group (at baseline); 160 participants total (at week 4); 83 in the Lacrinorm group (at week 4); 77 in the control group (at week 4) Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): Y, power 90% Reported subgroup analysis (Y/N): Y (age, duration of dry eye, and center)
Participants	Country: Belgium; France; Switzerland; United Kingdom Age (mean ± SD, range): 58.6 ± 16.2 years in the Lacrinorm group; 64.0 ± 14.0 years in the control group Gender: 17 men and 75 women in the Lacrinorm group; 14 men and 73 women in the control group Inclusion criteria: 1) age more than 18 years; 2) either sex; 3) aqueous-deficient dry eye defined as the presence of 2 from 4 specified symptoms (foreign body sensation, ocular dryness, burning or pain, and photophobia) and conformity with at least 2 of the following test results: (a) tear film break-up time of ≤ 10 secs; (b) fluorescein staining of ≥ 2 on a scale of 0 to 5; (c) Schirmer's test (without anesthesia) of ≤ 6 mm in 5 minutes; (d) lissamine green staining of ≥ 4 according to the criteria of van Bijsterveld (0 to 9) Exclusion criteria: 1) concomitant ocular pathology other than dry eye; 2) wearing of moisture-conserving spectacles or contact lenses; 3) use of ocular inserts for dry eye; 4) past history of intolerance or allergy to 1 of the study components (carbomer 940, cetrimide or benzalkonium chloride); 5) pregnancy Equivalence of baseline characteristics (Y/N): N (age; duration of dry eye)
Interventions	Intervention #1: 0.2% carbomer 940 with 0.01% benzalkonium chloride (Lacrinorm/GelTears, Laboratoire Chauvin) 4 times daily Intervention #2/control: 0.2% carbomer 940 with 0.01% cetrimide (Viscotears/Vidisic/Lacrigel) 4 times daily Length of follow-up: 4 weeks Notes: there was a washout period of a minimum of 7 days with preservative-free saline for participants using a tear substitute; systemic drugs were allowed before and during the trial, but the name and dosage were recorded; participants were asked to maintain the same levels of systemic therapy

Bron 1998a *(Continued)*

	throughout the study period or to inform the investigator of any change. If other drugs were instilled via the ocular route during the trial, this was considered to be a major protocol deviation
Outcomes	Primary outcome(s): symptoms (foreign body sensation, ocular dryness, burning or pain (including any stinging sensation), and photophobia) Secondary outcome(s): TBUT; lissamine green staining; fluorescein staining; Schirmer's test Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2 and 4 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	"The two treatments were supplied in identical, coded 10g tubes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The two treatments were supplied in identical, coded 10 g tubes"; "double-masked" trial, but it remains unclear if trial personnel was masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	19/179 (10.6%) were not included in the efficacy analysis; 10 in Lacrinorm group (5 consent withdrawn; 4 adverse events; 1 adverse event and worsening of the disease; 1 protocol violation); 9 in control group (4 consent withdrawn, 4 adverse event, 1 protocol violation)
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Baseline characteristics were not equivalent

Bron 1998b

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (2 sites)

Bron 1998b *(Continued)*

	Number randomized (total and per group): 90 participants total; 48 into the PAA group; 42 into the PVA group Unit of randomization (individual or eye): individual Exclusions after randomization: 7 in total; 5 in the PAA group (administrative problems); 2 in the PVA group (administrative problems) Losses to follow-up: 3 in the PAA group Number analyzed: 89 total (at baseline); 48 in PAA group (at baseline); 41 in the PVA group (at baseline); 80 total (at 6 weeks); 40 per group (at 6 weeks) Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: United Kingdom Age (mean ± SD, range): 59.6 ± 1.7 years in the PAA group; 58.8 ± 1.7 years in the PVA group Gender: 12 men and 36 women in the PAA group; 14 men and 27 women in the PVA group Inclusion criteria: 1) moderate dry eye defined as at least 2 of the following symptoms in both eyes: (a) gritty/foreign body sensation; (b) burning sensation; (c) dry eye sensation; (d) photophobia; and at least 1 of the following signs in both eyes: (a) Schirmer's test of ≤ 8 mm/5 minutes on the day of recruitment or ≤ 6 mm/5minutes already recorded in the hospital notes or tear break-up time of ≤ 10 secs Exclusion criteria: 1) age less than 18 years; 2) pregnancy or lactation; 3) known hypersensitivity to polyacrylic acid, cetrimide, polyvinyl alcohol or benzalkonium chloride; 4) systemic therapy which may induce corneal deposits or influence lacrimal secretion; 5) naso-lacrimal obstruction; 6) external eye disease including conjunctival inflammation and/or infection, corneal scars, corneal dystrophies and exophthalmos; 7) intraocular inflammation; 8) wearing of contact lens; 9) local treatment with eye drops and/or ointment other than for dry eye; 10) therapy-resistant dry eye; 11) participating in another trial Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (PAA group): 0.2% polyacrylic acid/carbomer with 0.01% cetrimide as preservative (Viscotears®) Intervention #2/control (PVA group): 1.4% polyvinyl alcohol with 0.01% benzalkonium chloride (Liquifilm®) Length of follow-up: 6 weeks Notes: there was a washout period of 7 days with preservative-free single-dose units of 0.9% sodium chloride for participants who were on treatment; participants were allowed to use drops as needed
Outcomes	Primary outcome(s): frequency of instillation Secondary outcome(s): symptoms (foreign body/gritty sensation; burning sensation; dry eye sensation; photophobia); conjunctival injection; ciliary injection; rose bengal staining; TBUT; Schirmer's test; drop tolerance Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 3 and 6 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported

Bron 1998b *(Continued)*

	Trial registration: not reported
	Funding source(s): not reported
	Conflicts of interest: 1 author was affiliated with a pharmaceutical company
	Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	10/90 (11.1%) were not included in the efficacy analysis; 8 in the PAA group (5 administrative problems; 3 lost to follow-up), and 2 in the PVA group (2 administrative problems)
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Participants were allowed to use drops as needed; one author was affiliated with a pharmaceutical company

Bruix 2006

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: single center
	Number randomized (total and per group): 19 participants total; 13 into the CMC group; 6 into the control group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: not reported
	Losses to follow-up: 2 in the CMC group; 6 in the control group
	Number analyzed: 19 participants total (at baseline); 13 in the CMC group (at baseline); 6 in the control group (at baseline)
	Unit of analysis (individual or eye): not reported
	Reported power calculation (Y/N): N

Bruix 2006 *(Continued)*

	Reported subgroup analysis (Y/N): N
Participants	Country: Spain Age (mean ± SD, range): 56.8 years, range 42 to 72 years in the CMC group; 62.0 years, range 52 to 72 years in the control group Gender: all women Inclusion criteria: 1) classified dry eye defined as fulfilling 1 to 4 criteria Exclusion criteria: 1) severe clinical symptoms; 2) inflammatory pathologies of the eye surface or in the anterior segment; 3) glaucoma; 4) wearing of contact lenses; 5) topical or systemic medication which could interfere in the production of tear; 6) eye surgery or eye trauma in the year prior to the beginning of the study Equivalence of baseline characteristics (Y/N): N (severity of disease)
Interventions	Intervention #1 (CMC group): 0.5% carboxymethylcellulose sodium without preservatives (Cellufresh®, Allergan SA) Intervention #2: placebo of balanced saline solution (Alcon-Cusi SA) Length of follow-up: 12 months Notes: participants were allowed to use 1 or 2 drops at least 3 - 4 times a day (or as needed); participants were not allowed to use any other type of topical eye medication during the trial
Outcomes	Primary outcome(s): symptoms; Schirmer's test; TBUT; fluorescein staining; rose bengal staining; tear meniscus height; conjunctival impression cytology; global functional assessment Secondary outcome(s): not distinguished Adverse events reported(Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 3, 6, and 12 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"a randomized inclusion protocol was utilized, in which patients involved in the trial were assigned in a ratio of 2:1 (treatment: control) by order of entry"; "We used table of inclusion in randomization (treatment – control – treatment)" (personal communication)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Bruix 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"masked-observer" trial; "Patients and personnel directly involved in the study were masked. The outcome assessor was not masked. BSS and active drug were conditioned in similar containers and grouped according to the number of randomization (patient 001 with vials marked 001 = treatment)" (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"masked-observer" trial; "Patients and personnel directly involved in the study were masked. The outcome assessor was not masked. BSS and active drug were conditioned in similar containers and grouped according to the number of randomization (patient 001 with vials marked 001 = treatment)" (personal communication)
Incomplete outcome data (attrition bias) All outcomes	High risk	"The mean clinical follow-up period was of 9 and a half months, ranging between 6 and 12 months."; "In the problem group one patient was lost at 6th and other at 9th months of follow-up. In the control group due to persistence of symptoms, 5 patients were followed just to 6th months and one more just to 9th months. Patients of control group were then treated." (personal communication)
Selective reporting (reporting bias)	High risk	Outcomes were reported incompletely; subjective symptoms were reported numerically in treatment group only
Other bias	Unclear risk	Baseline characteristics were not equivalent

Christensen 2004

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (7 sites) Number randomized (total and per group): 87 participants total; 42 into the Systane group; 45 into the Refresh Tears group Unit of randomization (individual or eye): individual Exclusions after randomization: none for intention-to-treat analysis; 3 participants in the Refresh tears discontinued due to adverse events Losses to follow-up: none Number analyzed: 87 participants total; 42 into the Systane group; 45 into the Refresh Tears group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): Y (corneal staining at baseline)
Participants	Country: United States Age (mean ± SD, range): 59.0 years total; 58.5 years in the Systane group; 59.5 years in the Refresh Tears group Gender: 10 men and 32 women in the Systane group; 15 men and 30 women in the Refresh Tears group Inclusion criteria: 1) desire to use eye drops; 2) sodium fluorescein corneal staining score of ≥ 3 (National Eye Institute (NEI) grid: sum of 5 areas per eye using a 0 (normal) to 3 (severe) scale) at screening (day 7) in the worst eye Exclusion criteria: not reported

Christensen 2004 *(Continued)*

	Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.4% polyethylene glycol 400 and 0.3% propylene glycol demulcents with hydroxypropyl guar as a gelling agent with 0.001% polyquad® as preservative (Systane™ Lubricant Eye Drops, Alcon Laboratories, Inc) 4 times daily Intervention #2: 0.5% carboxymethylcellulose sodium with Purite® as preservative (Refresh Tears® Lubricant Eye Drops, Allergan) 4 times daily Length of follow-up: 6 weeks Notes: there was a run-in period of 7 days with aqueous saline solution without polymers in both eyes 4 times per day
Outcomes	Primary outcome(s): conjunctival staining with a lissamine green; corneal fluorescein staining; symptoms; conjunctival injection; drop instillation comfort; LogMAR BCVA; slit-lamp findings Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 1, 2, 4, and 6 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "This research was funded by Alcon Research, Ltd." Conflicts of interest: 1 author was affiliated with a pharmaceutical company Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "Masking was maintained by relabeling all bottles and only the study coordinator interacted with study subjects concerning product use and compliance. Subjects were instructed not to discuss their assigned tear product with the doctors."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked" trial; "Masking was maintained by relabeling all bottles and only the study coordinator interacted with study subjects concerning product use and compliance. Subjects were instructed not to discuss their assigned tear product with the doctors."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All subjects randomized to treatment in the study were evaluable for safety and intent to treat analyses"; "Last observation carried forward method was used to input data for missed visits and discontinued subjects for the intent-to-treat data set."

Christensen 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Subjects were excluded if they had a low corneal staining score at baseline; 1 author was affiliated with a pharmaceutical company

Christensen 2009

Methods	Study design: randomized, parallel-group, controlled trial Study center: not reported Number randomized (total and per group): 105 participants total Unit of randomization (individual or eye): not reported Exclusions after randomization: not reported Losses to follow-up: not reported Number analyzed: not reported Unit of analysis (individual or eye): not reported Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: United States Age (mean ± SD, range): not reported Gender: not reported Inclusion criteria: 1) sum of corneal staining (NEI grid; max 15 points) of > 3; 2) need artificial tears at least some of the time Exclusion criteria: not reported Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.4% polyethylene glycol 400 and 0.3% propylene glycol (Systane® Ultra Lubricant Eye Drops, Alcon) 4 times daily Intervention #2: 0.9% glycerin and 0.5% carboxymethylcellulose sodium (Optive™, Allergan Inc) 4 times daily Length of follow-up: 6 weeks Notes: there was a washout period of 14 days with saline drop 4 times daily
Outcomes	Primary outcome(s): corneal staining; conjunctival staining; symptoms using a Treatment Satisfaction Questionnaire; VF-14 Questionnaire; TBUT Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2, 4 and 6 (at least)

Christensen 2009 *(Continued)*

	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: NCT00702377 Funding source(s): not reported Conflicts of interest: "Investigators are employees of Alcon Research Ltd" Publication language: English Notes: no full-text publication was available for this trial (abstract and clinical trial register forms only)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"A total of 105 patients were evaluable for intent-to-treat"; numbers randomized into each group were not reported"; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Authors were employed by pharmaceutical company; this trial was published in abstract form only

Cohen 2014

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (10 sites) Number randomized (total and per group): 147 participants total; 73 to the Systane group; 74 to the Refresh group Unit of randomization (individual or eye): individual Exclusions after randomization: 10 participants in total; 6 (3 participants' decision; 3 other reasons) in the Systane group; 4 (3 due to adverse events; 1 participant decision) in the Refresh group Losses to follow-up: none

Cohen 2014 *(Continued)*

	Number analyzed: 147 participants total; 73 to the Systane group; 74 to the Refresh group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): Y, power of 77% Reported subgroup analysis (Y/N): N
Participants	Country: United States Age (mean ± SD, range): 56.5 ± 15.0 years in the Systane group; 57.5 ± 16.6 years in the Refresh group Gender: 15 men and 58 women in the Systane group; 17 men and 57 women in the Refresh group Inclusion criteria:1) aged ≥ 18 years; 2) a sodium fluorescein corneal staining sum score ≥ 3 in either eye;3) BCVA of 0.6 logMAR or better in each eye; 4) use of a lubricant eye gel or ointment for dry eye at least once weekly over the previous month Exclusion criteria: 1) any ocular or systemic medical condition that may preclude safe administration of treatment or affect the results of the study, including inability to discontinue use of concomitant topical ocular drops during the study period; 2) previous ocular or intraocular surgery; 3) intolerance or hypersensitivity to any component in the study medications; 4) ocular infections within the last 30 days; 5) temporary punctal plugs; 6) permanent punctal plugs inserted ≤ 30 days before screening; 7) punctal occlusion performed ≤ 30 days before screening; 8) use of systemic medications that may contribute to dry eye (unless on a stable dosing regimen for ≥ 30 days before screening); 9) active iritis or uveitis; 10) unwillingness to discontinue contact lens wear starting 1 week or more before screening Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.4% polyethylene glycol 400, 0.3% propylene glycol, and hydroxypropyl guar (Systane®Gel Drops) 4 times daily Intervention #2: 1% carboxymethylcellulose sodium (Refresh LiquiGel® Drops) 4 times daily Length of follow-up: 6 weeks Notes: participants were required to have used a lubricant eye gel or ointment for dry eye at least once weekly over the previous month
Outcomes	Primary outcome(s): corneal staining with fluorescein Secondary outcome(s): conjunctival staining with lissamine green; TBUT; BCVA; Patient Global Assessment of Improvement; Impact of Dry Eye on Everyday Life (IDEEL); Treatmeant Satisfaction/Treatment Bother Questionnaire; Single Symptom Comfort Scale; Ocular Symptoms Questionnaire Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, week 1, 2, 4 and 6 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: between January 2011 and April 2011 Trial registration: not reported Funding source(s): "This study was funded by Alcon Laboratories Inc (Fort Worth, TX, USA). Medical writing support was provided by Peter A Rittenhouse of Complete Healthcare Communications Inc (Chadds Ford, PA, USA), and was funded by Alcon." Conflicts of interest: 1 author was affiliated with a pharmaceutical company Publication language: English

Cohen 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 (6.8%) participants discontinued trial; 6 (3 participant decision; 3 other reasons) in the Systane group, and 4 (3 due to adverse events; 1 participant decision) in the Refresh group; it is unclear how the missing data were handled "All 147 patients were included in the intent-to-treat/safety population. Missing data were not imputed."
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	1 author was affiliated with a pharmaceutical company

Comez 2013

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 43 participants total; 22 to the Systane and Eyestil group; 21 to the Tears Naturale and Refresh Tears group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: 13 participants total; 5 in the Systane and Eyestil group; 8 in the Tears Naturale and Refresh Tears group Number analyzed: 30 participants total; 17 in the Systane and Eyestil group; 13 in the Tears Naturale and Refresh Tears group Unit of analysis (individual or eye): individual (OSDI) and eye (other outcomes) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Turkey Age (mean ± SD, range): 47.4 ± 14.5 years, range 31 to 62 years in the Systane and Eyestil group; 46.3 ± 15.5 years, range 33 to 59 years in the Tears Naturale and Refresh Tears group

Comez 2013 *(Continued)*

	Gender: 10 men and 12 women in the Systane and Eyestil group; 9 men and 12 women in the Tears Naturale and Refresh Tears group Inclusion criteria:1) grade 2 or 3 (moderate or severe) dry eye syndrome according to the International Dry Eye Workshop grid Exclusion criteria: 1) contact lens wearers; 2) meibomian gland dysfunction; 3) receiving any topical eye drop or systemic drugs such as antihistamines or antidepressants Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (Systane and Eyestil group): 0.4% polyethylene glycol 400 and 0.3% propylene glycol (Systane®, Alcon Laboratories, Inc.) for the right eye and 15% sodium hyaluronate (Eyestil®, SIFI) for the left eye 5 times daily Intervention #2 (Tears Naturale and Refresh Tears group): 0.3% hydroxypropyl methylcellulose (Tears Naturale®, Alcon Laboratories, Inc.) for the right eye and 0.5% carboxymethylcellulose (Refresh® Tears, Allergan Inc.) 5 times daily Length of follow-up: 12 weeks Notes: each eye of a single participant was assigned to different artificial tears; participants for whom adherence was in doubt were excluded from the trial; participants with meibomian gland dysfunction were excluded, but participants with evaporative dry eye were included
Outcomes	Primary outcome(s): OSDI; tear osmolarity; Schirmer's test; TBUT Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y (none, personal communication) Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2, 4 and 12 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: between March and July 2011 Trial registration: not reported Funding source(s): "This research is funded by Canakkale Onsekiz Mart University, Scientific Research Project Center." Conflicts of interest: none Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors reported that they created a random number table by themselves without using computer system. (personal communication)
Allocation concealment (selection bias)	Low risk	"participants were prevented from foreseeing the assignment before and until they were assigned by using sequentially numbered containers" (personal communication)
Blinding of participants and personnel (performance bias) All outcomes	High risk	"single-masked" trial; "The medication received by the patients was labelled "group A right"' and "group A left" or "group B right" and "group B left" to preserve patient masking."; trial personnel were not masked

Comez 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	"single-masked" trial; "The medication received by the patients was labelled "group A right"' and "group A left" or "group B right" and "group B left" to preserve patient masking."; outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	High risk	13/43 (30.2%) participants (5 in the Systane and Eyestil group and 8 in the Tears Naturale and Refresh Tears group) were lost to follow-up and they were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	High risk	"each eye of a single participant was assigned to different artificial tears"; "the two eyes of each patient were considered as independent data points for further analysis."; participants were asked to dose the right eye first although they used different study medications in each eye

Davitt 2010

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (8 sites) Number randomized (total and per group): not explicitly reported Unit of randomization(individual or eye): individual Exclusions after randomization: 2 participants in total; 2 in the control group discontinued due to adverse events Losses to follow-up: not reported Number analyzed: 105 participants total; 52 in the treatment group; 53 in the control group Unit of analysis (individual or eye): individual Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: United States Age (mean ± SD, range): 33 participants between 18 to 64 years, and 19 participants 65 years or older in the treatment group; 41 participants between 18 and 64 years, and 12 participants 65 years or older in the control group Gender: 13 men and 39 women in the treatment group; 15 men and 38 women in the control group Inclusion criteria: 1) either sex; 2) any race or ethnicity; 3) 18 years of age or older; 4) dry eye presented at screening (day -14) with a sodium fluorescein corneal staining score of ≥ 3 in either eye by using the NEI staining grid; 5) a response in the Symptom Eligibility Questionnaire of at least "some of the time" to the question, "How often have your eyes felt dry enough to want to use eye drops?" Exclusion criteria: 1) wearing of contact lenses for at least 1 week before visit 1 as well as during the study; 2) use of medications that could have interfered with study participation or treatment evaluation; 3) any concurrent disease or condition that could have complicated or interfered with the administration or evaluation of the study drug Equivalence of baseline characteristics (Y/N): Y

Davitt 2010 *(Continued)*

Interventions	Intervention #1: polyethylene glycol 400, propylene glycol, and hydroxypropyl guar (Alcon Research Ltd) 4 times daily Intervention #2: 0.5% carboxymethylcellulose and 0.9% glycerin (Optive™ Lubricant Eye Drops, Allergan) 4 times daily Length of follow-up: 6 weeks Notes: there was a run-in period of 2 weeks with an aqueous saline solution without polymers (relabeled Sensitive Eyes® Drops, Baush and Lomb) 4 times daily; participants were not allowed to use contact lenses during trial
Outcomes	Primary outcome(s): ocular symptoms questionnaire; OSDI; VF-14; corneal staining; conjunctival staining; TBUT Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 1, 2, 4, and 6 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: enrollment between 2007 and 2008 Trial registration: not reported Funding source(s): "Mike Christensen, Marion Tudor, and Anna E. Martin (Alcon Laboratories, Inc.) managed the conduct of this study." Conflicts of interest: "Dr. Christensen and Anna E. Martin are employees of Alcon Research, Ltd. Alcon Research, Inc., assisted with analysis of the data and with preparation of this article." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "study drugs were dispensed to all patients in identical packaging, and designated study personnel who were not involved with the study evaluations dispensed, collected, and accounted for all study drugs. The patients, the study staff, the investigators, the sponsor, and the monitors were unaware of each individual patient's assigned treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked" trial; "study drugs were dispensed to all patients in identical packaging, and designated study personnel who were not involved with the study evaluations dispensed, collected, and accounted for all study drugs. The patients, the study staff, the investigators, the sponsor, and the monitors were unaware of each individual patient's assigned treatment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The intent-to-treat (ITT) population comprised all patients who received randomized treatment and had at least one on therapy study visit."; "Overall, 113 adult patients with a diagnosis of dry eye were enrolled at 8 investigational sites in the United States. The results of 105 patients (ITT data set) who were

Davitt 2010 *(Continued)*

		randomized to Test Product (n = 52) or Control Product (n = 53) are reported herein."; it was unclear if the 8 participants were randomized or not; the reasons why the 8 participants were excluded were not provided; number of participants who completed the trial was not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	2 authors were affiliated with a pharmaceutical company

Donshik 1998 Trial 1

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 27 participants total; number per group was not reported Unit of randomization(individual or eye): individual Exclusions after randomization: not reported Losses to follow-up: not reported Number analyzed: not reported Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: not reported Age (mean ± SD, range): 51.8 years, range 26 to 72 years Gender: not reported Inclusion criteria: 1) moderate to severe case of keratoconjunctivitis sicca defined as (a) Schirmer's tests of ≤ 5 mm/ 5 minutes; (b) positive rose bengal staining of ≥ 3 out of 9; (c) conjunctival impression cytology mean score of 3 out of 9 for the bulbar conjunctiva and < 1 out of 3 for the palpebral conjunctiva Exclusion criteria: 1) wearing of contact lenses; 2) ocular surgery within the past 6 months; 3) active infection or inflammatory disease not related to keratoconjunctivitis sicca; 4) any corneal abnormalities unrelated to keratoconjunctivitis sicca Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.3% hydroxypropyl methylcellulose, dextran 70, and 0.1% electrolytes with bicarbonate (BION Tears, Alcon Laboratories) Intervention #2: 0.3% hydroxypropyl methylcellulose, dextran 70, and 0.1% electrolytes without bicarbonate Length of follow-up: 56 days Notes: frequency of artificial tear usage was not reported; participants were not allowed to use any ocular medication during trial; participants could not have taken any concomitant systemic medication for < 1 month prior to being entered into the trial, and their dose regimens could not be changed during the course of the trial

Donshik 1998 Trial 1 *(Continued)*

Outcomes	Primary outcome(s): rose bengal staining; impression cytology Secondary outcome(s): signs and symptoms Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, days 7, 28 and 56 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Research supported by Alcon Laboratories, Fort Worth, TX" Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label" trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number randomized to each group, number excluded or lost to follow-up, and number analyzed were not reported
Selective reporting (reporting bias)	High risk	Data were reported incompletely; data on days 7 and 28 were not reported
Other bias	Unclear risk	This trial was funded by a pharmaceutical company

Donshik 1998 Trial 2

Methods	Study design: 3-arm randomized, parallel-group, controlled trial Study center: multicenter (number of sites not reported) Number randomized (total and per group): 41 participants in total; 14 into the BION Tears group; 13 into the AquaSite group; 14 into the Cellufresh group Unit of randomization (individual or eye): individual

Donshik 1998 Trial 2 *(Continued)*

	Exclusions after randomization: not reported Losses to follow-up: not reported Number analyzed: not reported Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: not reported Age (mean ± SD, range): 52 years, range 30 to 82 years Gender: not reported Inclusion criteria: 1) moderate to severe case of keratoconjunctivitis sicca defined as (a) Schirmer's tests of ≤ 5 mm/5 minutes; (b) positive rose bengal staining of ≥ 3 out of 9; (c) conjunctival impression cytology mean score of 3 out of 9 for the bulbar conjunctiva and < 1 out of 3 for the palpebral conjunctiva Exclusion criteria: 1) wearing of contact lenses; 2) ocular surgery within the past 6 months; 3) active infection or inflammatory disease not related to keratoconjunctivitis sicca; 4) any corneal abnormalities unrelated to keratoconjunctivitis sicca Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1 (BION Tears group): 0.3% hydroxypropyl methylcellulose, dextran 70, and 0.1% electrolytes with bicarbonate (BION Tears, Alcon Laboratories) Intervention #2 (AquaSite group): 0.2% polyethylene glycol 400 (AquaSite, Ciba Vision Ophthalmics) Intervention #3 (Cellufresh group): 0.5% carboxymethylcellulose sodium (Cellufresh, Allergan Pharmaceuticals) Length of follow-up: 84 days Notes: there was a washout period of 1 to 2 weeks with Refresh; frequency of artificial tear usage was not reported; participants were not allowed to use any ocular medication during trial; participants could not have taken any concomitant systemic medication for < 1 month prior to being entered into the trial, and their dose regimens could not be changed during the course of the trial
Outcomes	Primary outcome(s): rose bengal staining; impression cytology; comfort; acceptability Secondary outcome(s): signs and symptoms Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, days 21, 42, 63, and 84 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Research supported by Alcon Laboratories, Fort Worth, TX" Conflicts of interest: not reported Publication language: English

Donshik 1998 Trial 2 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number excluded or lost to follow-up, and number analyzed were not reported
Selective reporting (reporting bias)	High risk	Data were reported incompletely; data on days 21, 42, and 63 were not reported
Other bias	Unclear risk	This trial was funded by a pharmaceutical company

Donshik 1998 Trial 3

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (number of sites not reported) Number randomized (total and per group): 124 participants in total; 61 into the BION Tears group; 63 into the Refresh Plus group Unit of randomization(individual or eye): individual Exclusions after randomization: not reported Losses to follow-up: not reported Number analyzed: not reported Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: not reported Age (mean ± SD, range): 56 years, range 24 to 82 years Gender: not reported Inclusion criteria: 1) moderate to severe case of keratoconjunctivitis sicca defined as (a) Schirmer's tests of ≤ 5 mm/5 minutes; (b) positive rose bengal staining of ≥ 3 out of 9; (c) conjunctival impression

Donshik 1998 Trial 3 *(Continued)*

	cytology mean score of 3 out of 9 for the bulbar conjunctiva and < 1 out of 3 for the palpebral conjunctiva Exclusion criteria: 1) wearing of contact lenses; 2) ocular surgery within the past 6 months; 3) active infection or inflammatory disease not related to keratoconjunctivitis sicca; 4) any corneal abnormalities unrelated to keratoconjunctivitis sicca Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1 (BION Tears group): 0.3% hydroxypropyl methylcellulose, dextran 70, and 0.1% electrolytes with bicarbonate (BION Tears, Alcon Laboratories) Intervention #2 (Refresh Plus group): 0.5% carboxymethylcellulose sodium (Refresh Plus, Allergan Inc) Length of follow-up: 84 days Note: there was a washout period of 1 to 2 weeks with Refresh; frequency of artificial tear usage was not reported; participants were not allowed to use any ocular medication during trial; participants could not have taken any concomitant systemic medication for < 1 month prior to being entered into the trial, and their dose regimens could not be changed during the course of the trial
Outcomes	Primary outcome(s): rose bengal staining; impression cytology; comfort; acceptability Secondary outcome(s): signs and symptoms Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, days 21, 42, 63, and 84 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Research supported by Alcon Laboratories, Fort Worth, TX" Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias)	Unclear risk	Number excluded or lost to follow-up, and number analyzed were not reported

Donshik 1998 Trial 3 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Data were reported incompletely; data on days 21, 42, and 63 were not reported
Other bias	Unclear risk	This trial was funded by a pharmaceutical company

Dumbleton 2009

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 110 participants in total; 56 into the treatment group; 54 into the control group Unit of randomization (individual or eye): individual Exclusions after randomization: 3 participants in total; 1 in the treatment group (due to a recurrent epithelial erosion, which had originally occurred prior to study entry); 2 in the control group (due to ocular headaches combined with a reported change in taste after drop instillation, and self-reported perception of redder eyes) Losses to follow-up: 3 participants total; 3 in the treatment group (a sports injury that prevented attending follow-up visits, a geographic relocation, and an inability to attend the final follow-up visit) Number analyzed: 104 participants total; 52 per group Unit of analysis (individual or eye): individual (right eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Canada Age (mean ± SD, range): 46.8 ± 19.1 years, range 18 to 86 years total; 46.3 ± 19.3 years, range 19 to 78 years in the treatment group; 47.2 ± 19.1 years, range 18 to 86 years in the control group Gender: 13 men and 43 women in the treatment group; 15 men and 39 women in the control group Inclusion criteria: 1) symptoms of a dry eye (dryness, gritty or sandy sensation, and burning); 2) regular users (every day) of ocular lubricants Exclusion criteria: 1) current contact lens wearers; 2) using any systemic or topical medications that may affect ocular health; 3) any history of ocular surgery, other than cataract surgery, within the past 12 months (i.e. refractive surgery, penetrating keratoplasty, and so forth); 4) diagnosed with Sjogren' syndrome; 5) pregnant or lactating Equivalence of baseline characteristics (Y/N): N (number of habitual drops used)
Interventions	Intervention #1: 0.25% polyethylene glycol 400 with sodium chlorite (Ocupure) as preservative (Blink® gel tears, Advanced Medical Optics) Intervention #2/control: 1.0% carboxymethylcellulose sodium with Purite as preservative (Refresh Liquigel®, Allergan) Length of follow-up: 30 days Notes: participants were allowed to use drops as needed; there was no washout period before trial although participants were regular user of ocular lubricants

Dumbleton 2009 *(Continued)*

Outcomes	Primary outcome(s): SESOD; OSDI; study-specific ocular symptoms questionnaire (SQ); TBUT; phenol red thread test; tear meniscus height; fluorescein staining; lissamine green staining; LogMAR visual acuity Secondary outcome(s): not distinguished Adverse events reported(Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, days 7, 15, and 30 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Supported by Advanced Medical Optics, Inc." Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "To maintain masking of both the subjects and the investigators, all identifying labels were removed from the ocular lubricants and replaced with a coded label. An ophthalmic assistant dispensed the ocular lubricants according to a randomization table"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked" trial; "To maintain masking of both the subjects and the investigators, all identifying labels were removed from the ocular lubricants and replaced with a coded label. An ophthalmic assistant dispensed the ocular lubricants according to a randomization table"
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of six subjects were discontinued during the study, four in the test group and two in the control group"; 6/110 (5.5%) were not included in the analysis
Selective reporting (reporting bias)	High risk	Outcomes were reported incompletely "There were no adverse events or notable clinical occurrences during the course of the study in the test or the control groups and therefore results for the objective assessments are not reported in detail in this article"
Other bias	Unclear risk	Participants were allowed to use drops as needed and the number of habitual drops used was significantly different between groups at baseline; there was no washout period before trial although participants were regular user of ocular lubricants; this trial was supported by a pharmaceutical company

Foley-Nolan 1995

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: not reported
	Number randomized (total and per group): 91 participants
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: not reported
	Losses to follow-up: not reported
	Number analyzed: 80 participants; 40 per group
	Unit of analysis (individual or eye): individual
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: United Kingdom
	Age (mean ± SD, range): not reported
	Gender: not reported
	Inclusion criteria: 1) dry eye
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.2% polyacrylic acid (Viscotears)
	Intervention #2: 1.4% polyvinyl alcohol
	Length of follow-up: 6 weeks
	Notes: none
Outcomes	Primary outcome(s): drops used daily; total signs and symptoms score; local tolerance
	Secondary outcome(s): not distinguished
	Adverse events reported (Y/N): Y
	Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 3 and 6
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: not reported
	Funding source(s): not reported
	Conflicts of interest: not reported
	Publication language: English
	Notes: this trial was published in abstract form only
Risk of bias	

Foley-Nolan 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"single-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"single-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomized into each group were not reported; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was published in abstract form only

Garcia-Lazaro 2011

Methods	Study design: randomized, cross-over, controlled trial Study center: single center Number randomized (total and per group): 20 participants total; 10 per group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: none Number analyzed: 20 participants in total; 10 per group Unit of analysis (individual or eye): individual (right eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Spain Age (mean ± SD, range): 57.5 ± 8.4 years total Gender: 12 men and 8 women Inclusion criteria: 1) dry eye on the basis of significant subjective dry eye symptoms (McMonnies test score > 14), Schirmer's test results of < 5 mm/5 minutes without anesthesia), and TBUT of < 5 secs; 2) ocular surface abnormalities diagnosed through positive results on either corneal fluorescein staining or corneal and conjunctival rose bengal staining scores of ≥ 3

Garcia-Lazaro 2011 *(Continued)*

	Exclusion criteria: 1) unilateral dry eye; 2) pregnant or lactating women; 3) ocular surgery of any type or ocular trauma within the previous 4 months prior to enrolment; 4) abnormality of the nasolacrimal drainage apparatus; 5) permanent occlusion of lacrimal puncta in any eye; 6) use of a temporary punctual plug; 7) wearing of contact lens; 8) known hypersensitivity to any of the components or procedures used in the study Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.25% polyethylene glycol 400 and sodium hyaluronate with Ocupure as preservative (Blink Intensive Tears, Abbott Medical Optics Inc), 3 times daily Intervention #2: 0.3% hypromellose with cetrimide as preservative (Artific Tears, Farma-Lepori SA), 3 times daily Length of follow-up: 1 month in each phase Notes: there was a washout period of 7 days between 2 phases
Outcomes	Primary outcome(s): tear meniscus height Secondary outcome(s): none Adverse events reported (Y/N): Y (personal communication) Measurements taken, specify intervals at which outcomes assessed: baseline, month 1 in each phase Other issues with outcome assessment (e.g. quality control for outcomes if any): all measurements were taken in the same room where the temperature was kept constant at between 21°C and 23°C and humidity between 45% and 65%
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random sequence generation was made referring to a random number table" (personal communication)
Allocation concealment (selection bias)	Unclear risk	"the boxes were coded (numbered)" (personal communication)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both participants and examiners were masked" (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Both participants and examiners were masked" (personal communication); "All measurements were taken under the same conditions of illumination...This was carried out manually by a single masked observer"
Incomplete outcome data (attrition bias)	Low risk	There were no missing data

Garcia-Lazaro 2011 *(Continued)*

All outcomes

Selective reporting (reporting bias)	High risk	Data were reported incompletely
Other bias	Unclear risk	This trial was a cross-over design with a 1-week washout period between the 2 phases; data were not separately reported in each phase

Grene 1992

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 56 participants total Unit of randomization (individual or eye): individual Exclusions after randomization: 2 in total; 2 in the CMC group (1 due to noncompliance; 1 due to blurring and discomfort) Losses to follow-up: not reported Number analyzed: not reported Unit of analysis (individual or eye): individual Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: United States Age (mean ± SD, range): not reported Gender: not reported Inclusion criteria: 1) keratoconjunctivitis sicca; 2) either (a) Schirmer test of ≤ 2 mm, (b) Schirmer's test of ≤ 5 mm and ≥2 superficial punctuate keratitis in 2 of 5 exposure zones, or (c) Schirmer's test of ≤ 5 mm and 3 of the following symptoms: burning/stinging, foreign body sensation, photophobia, or dryness of at least 2+ severity on a scale of 0 - 4 Exclusion criteria: 1) blepharitis or any other active ocular disease; 2) any uncontrolled systemic disease; 3) history of herpetic keratitis; 4) wearing of contact lenses; 5) recent ocular surgery or trauma Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (CMC group): 1.0% carboxymethylcellulose sodium (Celluvisc Lubricant Ophthalmic solution, Allergan Pharmaceuticals) 8 times daily Intervention #2/control: 0.3% hydroxypropyl methylcellulose with polyquanternium-1 as preservative (Tears Naturale 2 Lubricant Eye Drops, Alcon Laboratories) 8 times daily Length of follow-up: 8 weeks Notes: there was a run-in period of 4 weeks with 0.3% carboxymethylcellulose 8 times daily; participants were not permitted to use systemic antihistamines, other medication with anticholinergic effects, or topical ophthalmic medications other than the study medication during the trial
Outcomes	Primary outcome(s): Schirmer's test; corneal fluorescein staining; conjunctival staining; impression cytology; symptoms

Grene 1992 *(Continued)*

	Secondary outcome(s): none
	Adverse events reported (Y/N): Y
	Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 1, 4, and 8
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: not reported
	Funding source(s): "This work was sponsored by Allergan Pharmaceuticals"
	Conflicts of interest: not reported
	Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "Patients began treatment with their randomly assigned, unit-dose, masked medication"; "Both medications were packed in identical unit-dose dispensers"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-masked" trial, but if outcome assessor was masked this was not reported explicitly
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/56 (3.6%) in the CMC group were excluded due to noncompliance, or blurring and discomfort; number randomized and analyzed was not reported; number of participants who were lost to follow-up was not reported
Selective reporting (reporting bias)	High risk	Data were reported incompletely; not all symptoms scores were included in table
Other bias	Unclear risk	This trial was funded by a pharmaceutical company

Huth 2008

Methods	Study design: randomized, cross-over, controlled trial
	Study center: not reported
	Number randomized (total and per group): not reported
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: not reported
	Losses to follow-up: not reported

Huth 2008 *(Continued)*

	Number analyzed: 22 participants
	Unit of analysis (individual or eye): individual (right eye)
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: United States
	Age (mean ± SD, range): range 26 to 72 years
	Gender: men and women, but numbers were not reported
	Inclusion criteria: 1) reported dry eye symptoms
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.25% polyethylene glycol 400 (Blink Tears® Lubricant Eye Drops, Advanced Medical Optics Inc)
	Intervention #2: 0.4% polyethylene glycol 400 and 0.3% propylene glycol (Systane® Lubricant Eye Drops, Alcon)
	Length of follow-up: 14 days
	Notes: there was a washout period of 3 - 4 days between treatment periods in cross-over design (personal communication)
Outcomes	Primary outcome(s): tear film thickness; time to return baseline after drop instillation
	Secondary outcome(s): not distinguished
	Adverse events reported (Y/N): Y (personal communication)
	Measurements taken, specify intervals at which outcomes assessed: days 1, and 14
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: provided IRB number (www.rcrc-irb.com PEGT-102-9582)
	Funding source(s): not reported
	Conflicts of interest: authors were affiliated with a pharmaceutical company
	Publication language: English
	Notes: this trial was published in abstract form only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization codes were obtained by random number-generating computer software" (personal communication)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Huth 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; All study products were over-labeled with generic white labels with study information only (personal communication); participants and the outcome assessors were masked to which study product was being used (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked" trial; participants and the outcome assessors were masked to which study product was being used (personal communication)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomized into each group were not reported; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was a cross-over design; this trial was not published in full-text

Iester 2000

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (3 sites) Number randomized (total and per group): 135 participants total Unit of randomization (individual or eye): individual Exclusions after randomization: 17 participants total (6 participants had tear fering patterns I and II at time 0; 4 had bengal rose allergy; 7 other reasons) Losses to follow-up: 5 participants Number analyzed: 113 participants total; 58 in the hyaluronic acid group; 55 in the HPMC group Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Italy Age (mean ± SD, range): 52.2 ± 10.6 years in the hyaluronic acid group; 56.4 ± 12.8 years in the HPMC group Gender: 10 men and 103 women; 4 men and 54 women in the hyaluronic acid group; 6 men and 49 women in the HPMC group Inclusion criteria: 1) Schirmer's test < 5.5 mm/5 minutes; 2) rose bengal staining positive and typical; 3) TBUT < 7 secs; 4) typical KCS symptoms Exclusion criteria: 1) infectious keratoconjunctivitis or inflammatory disease not related to dry eye; 2) previous ocular surgery; 3) concomitant ocular pathologies; 4) eyelid or eyelashes abnormalities; 5) nasolacrimal apparatus alteration; 6) consumption of drugs affecting tearing; 7) concomitant ocular therapies; 8) pregnancy Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.4% hyaluronic acid 6 times daily

Iester 2000 *(Continued)*

	Intervention #2: 0.3% hydroxypropyl methylcellulose 6 times daily Length of follow-up: 60 days Notes: there was a 5 - 10 day washout period using unpreserved saline as needed
Outcomes	Primary outcome(s): subjective symptoms of dry eye; Schirmer's test; TBUT; ocular surface rose bengal staining; ocular surface fluorescein staining; tear fering test; tear osmolarity; conjunctival impression cytology Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, days 15, 30 and 60 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "The study was a multicentre trial conducted in Italy by Fidia Oftal spa, Catania, Italy." Conflicts of interest: "M.I., G.J.O., G.G., P.M. and M. R. have no proprietary interest in development or marketing of any product mentioned in this article. M.T, and S.G. are employees of FIDIA Oftal." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Masking of participants and personnel was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of outcome assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	22/135 (16.3%) were either lost to follow-up or excluded, and they were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	High risk	This trial was funded by industry; 2 authors were affiliated with industry; the enrolled participants were stopped at different time points (60 or 90 days)

Johnson 2008

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 65 participants in total; 33 into the carbomer group; 32 into the sodium hyaluronate group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: none Number analyzed: 65 participants in total; 33 in the carbomer group; 32 in the sodium hyaluronate group Unit of analysis (individual or eye): individual (1 eye was randomly selected) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: United Kingdom Age (mean ± SD, range): median 38 years, range 21 to 64 years total; median 36 years in the carbomer group; median 39 years in the sodium hyaluronate group Gender: not reported Inclusion criteria: 1) moderate dry eye defined as TBUT < 10 secs, staining of the cornea with fluorescein and bulbar conjunctiva with lissamine green between grades 1 and 3 with the logarithmic Oxford scheme Exclusion criteria: not reported Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.3% carbomer 934 (Lacryvisc, Alcon) from 2 to 8 times daily Intervention #2: 0.18% sodium hyaluronate (Vismed, TRB Chemedica AG) from 2 to 8 times daily Length of follow-up: 1 month Notes: there was a run-in period of 7 to 14 days with unpreserved 0.9% saline (Unilarm, CIBA Vision Ophthalmics) as required, up to 4 times a day in both eyes; participants were asked to refrain from using treatments for at least 4 hour before every visit
Outcomes	Primary outcome(s): Ocular comfort index (OCI); NIBUT; TBUT; fluorescein staining; lissamine green staining; number of drops used Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, month 1 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "This study was sponsored by TRB Chemedica, Geneva, Switzerland. Michael Johnson was additionally supported by a research scholarship from Ultralase Ltd."

Johnson 2008 *(Continued)*

	Conflicts of interest: not reported
	Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"These were relabeled to give them a very similar appearance, and were allocated in a double-masked manner using block randomization to ensure nearly equal group numbers"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"These were relabeled to give them a very similar appearance, and were allocated in a double-masked manner using block randomization to ensure nearly equal group numbers", but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"These were relabeled to give them a very similar appearance, and were allocated in a double-masked manner using block randomization to ensure nearly equal group numbers", but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was funded by industry; "Instructions were given to use the tear substitutes as symptoms dictated with a minimum of two and maximum of eight instillations in both eyes, every day for 28 ± 3 days"

Khanal 2007

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: single center
	Number randomized (total and per group): 53 participants in total; 26 in the hypromellose group; 27 in the castor oil group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: none
	Losses to follow-up: none
	Number analyzed: 53 participants in total; 26 in the hypromellose group; 27 in the castor oil group
	Unit of analysis (individual or eye): individual
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: United Kingdom

Khanal 2007 *(Continued)*

	Age (mean ± SD, range): 37 years Gender: 12 men and 41 women Inclusion criteria: 1) positive symptoms ≥ 2 in the McMonnies Dry Eye Questionnaire; 2) mild to moderate dry eye defined as noninvasive TBUT of 5 to 10 secs or Schirmer's test without anesthesia of 2 to 5 mm in 5 minutes Exclusion criteria: 1) wearing of contact lenses; 2) any ocular surface disorders other than dry eye; 3) systemic conditions likely to affect the tear film Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.32% hypromellose (Artelac Single Dose Unit, Dr. Mann Pharma), 3 times daily Intervention #2: 1.25% castor oil (Allergan), 3 times daily Length of follow-up: 30 days Notes: none
Outcomes	Primary outcome(s): lipid film structure and stability; tear evaporation; turnover; osmolarity Secondary outcome(s): none Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and day 30 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "Supported by an unrestricted educational grant from Allergan Inc." Conflicts of interest: 1 author was affiliated with a pharmaceutical company Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias)	Low risk	There were no missing data

Khanal 2007 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was funded by a pharmaceutical company; 1 author was affiliated with a pharmaceutical company

Kislan 2008

Methods	Study design: randomized, cross-over, controlled trial
	Study center: not reported
	Number randomized (total and per group): 80 eyes of 40 participants (it is unclear if this number is number randomized or number analyzed)
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: not reported
	Losses to follow-up: not reported
	Number analyzed: 80 eyes of 40 participants (it is unclear if this number is number randomized or number analyzed)
	Unit of analysis (individual or eye): not reported
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: not reported
	Age (mean ± SD, range): not reported
	Gender: not reported
	Inclusion criteria: not reported
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: polyethylene glycol 400-based artificial tears 4 times daily
	Intervention #2: hydroxypropyl guar based artificial tears 4 times daily
	Length of follow-up: 1 month in each treatment phase
	Notes: none
Outcomes	Primary outcome(s): TBUT; lissamine green staining; symptoms; visual acuity
	Secondary outcome(s): not distinguished
	Adverse events reported (Y/N): N
	Measurements taken, specify intervals at which outcomes assessed: baseline, and month 1 in each phase

Kislan 2008 *(Continued)*

	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English Notes: this trial was published in abstract form only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomized into each group were not reported; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was a cross-over design; this trial was funded by a pharmaceutical company; this trial was published in abstract form only

Lanz 2006

Methods	Study design: randomized, cross-over, controlled trial Study center: single center Number randomized (total and per group): not reported Unit of randomization(individual or eye): individual Exclusions after randomization: not reported Losses to follow-up: not reported Number analyzed: 37 participants

Lanz 2006 *(Continued)*

	Unit of analysis (individual or eye): not reported
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: not reported
	Age (mean ± SD, range): 49.8 ± 14.1 years, range 22 to 74 years
	Gender: 9 men and 28 women
	Inclusion criteria: moderate to severe dry eye
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.3% hypromellose with sodium perborate (GenAqua®) as preservative (GenTeal®, Novartis Ophthalmics)
	Intervention #2: 0.3% hypromellose without preservative (Tears Naturale® Single Dose Unit, Alcon)
	Length of follow-up: 4 weeks in each treatment phase
	Notes: none
Outcomes	Primary outcome(s): sign (Schirmer's test; TBUT; corneal staining); symptoms (tired eyes; dryness; foreign body sensation; burning)
	Secondary outcome(s): not distinguished
	Adverse events reported (Y/N): N
	Measurements taken, specify intervals at which outcomes assessed: baseline, week 4 in each treatment phase
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: not reported
	Funding source(s): not reported
	Conflicts of interest: "Business Unit Ophthalmics, Novartis Pharma AG, Basel, Switzerland"
	Publication language: English
	Notes: this trial was published in abstract form only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias)	High risk	"open-label" trial

Lanz 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label" trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomized into each group were not reported; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was a cross-over design; this trial was published in abstract form only

Lee 2011

Methods	Study design: randomized, parallel-group, controlled trial Study center: single center Number randomized (total and per group): 67 participants total; 34 participants into the sodium hyaluronate group; 33 into the CMC group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: 2 participants in the sodium hyaluronate group Number analyzed: 65 participants total; 32 participants in the sodium hyaluronate group; 33 in the CMC group Unit of analysis (individual or eye): not reported Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: South Korea Age (mean ± SD, range): 37 ± 13.4 years, range 21 to 66 years in the sodium hyaluronate group; 39 ± 14.6 years, range 21 to 70 years in the CMC group Gender: 2 men and 30 women in the sodium hyaluronate group; 4 men and 29 women in the CMC group Inclusion criteria: 1) presence of subjective symptoms; 2) TBUT < 10 secs at least in 1 eye; 3) a fluorescein-staining score ≥ 3 at least in 1 eye Exclusion criteria: 1) a history of previous ocular or intraocular surgery; 2) evidence of acute or chronic infections or an inflammatory condition of the cornea and conjunctiva; 3) history of intolerance or hypersensitivity to any component of the study medications; 4) use of topical ocular medications; 5) unwillingness to discontinue contact lens use during the study period; 6) presence of current punctal occlusion Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.1% sodium hyaluronate (Hynex, Alcon Laboratory) 6 times daily Intervention #2: 0.5% carboxymethyl cellulose (Refresh Plus, Allegan) 6 times daily

Lee 2011 *(Continued)*

	Length of follow-up: 8 weeks Notes: none
Outcomes	Primary outcome(s): subjective symptoms of dry eye; TBUT; corneal staining with fluorescein; conjunctival staining with fluorescein Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 4 and 8 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: December 2008 to May 2009 Trial registration: not reported Funding source(s): "Supported partially by a faculty research grant of Yonsei University College of Medicine for 2009 and Alcon Laboratory, Seoul, Korea" Conflicts of interest: "The authors have no proprietary interests in any of the products discussed in this article." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"observer-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"observer-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2/67 (3%) were lost to follow-up, and were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Marner 1996

Methods	Study design: randomized, cross-over, controlled trial

Marner 1996 *(Continued)*

	Study center: multicenter (7 sites) Number randomized (total and per group): 61 participants total; number randomized to each group was not reported Unit of randomization (individual or eye): individual Exclusions after randomization: 6 participants in total; 4 during the carbomer phase, and 1 during the PVA phase discontinued due to adverse events; 1 was excluded due to protocol violation Losses to follow-up: none Number analyzed: 55 participants total Unit of analysis (individual or eye): individual (paired-eye design) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Denmark Age (mean ± SD, range): 64.3 years, range 38 to 89 years Gender: 10 men and 51 women Inclusion criteria: 1) 1 or several of the following symptoms of dry eye: a) dryness; b) burning; c) foreign body sensation; d) photophobia; e) pain; f) difficulty in opening eyes after sleeping; 2) at least 1 of the following signs of dry eye in both eyes: a) Schirmer test result of < 10 mm/5 minutes; b) TBUT < 10 secs; c) rose bengal staining score of > 3 (Bijsterveld score range 0 - 9 for each eye) Exclusion criteria: 1) ocular infection in previous week; 2) ocular surgery or trauma in the previous 2 months; 3) wearing of contact lens in the previous 2 months; 4) use of eye medication other than artificial tears in the previous 2 months; 5) treatment with drugs known to affect mucous membranes; 6) corneal haze Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (carbomer phase): carbomer-containing viscous gel (Lubrithal®, Leo pharmaceutical Products) Intervention #2/control (PVA phase): 1.4% polyvinyl alcohol (Lacril®/Liquifilm®, Allergan) Length of follow-up: 2 weeks in each phase Notes: there was no washout period between 2 treatment phases; participants were allowed to use study medications as needed, but not 2 hours before evaluation at study visits; number of daily ocular instillation of current treatment at baseline was comparable; mean number of instillation per day was 3.9 in the carbomer phase and 4.6 in the PVA phase at the end of each phase
Outcomes	Primary outcome(s): symptoms; Schirmer's test; fluorescein staining; TBUT; rose bengal staining; frequency of application Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and week 2 in each phase Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported

Marner 1996 *(Continued)*

	Funding source(s): not reported
	Conflicts of interest: not reported
	Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open" trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open" trial
Incomplete outcome data (attrition bias) All outcomes	High risk	6/61 (9.8%) were excluded (4 during the carbomer phase, and 1 during the PVA phase discontinued due to adverse events; 1 was excluded due to protocol violation), and were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Cross-over design without a washout period between 2 phases; "Tests for carry-over and period effects did not reveal any results which would have influenced the estimated treatment effect"; participants were allowed to use study medications as needed, but frequency of daily instillation was addressed

Nelson 1988

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: multicenter (2 sites)
	Number randomized (total and per group): 36 participants total; 20 participants into the sodium hyaluronate group; 16 into the polyvinyl alcohol group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: none
	Losses to follow-up: 1 in the polyvinyl alcohol group (withdrew because of dissatisfaction with the treatment)
	Number analyzed: 35 participants total; 20 participants in the sodium hyaluronate group; 15 in the polyvinyl alcohol group
	Unit of analysis (individual or eye): individual
	Reported power calculation (Y/N): N

Nelson 1988 *(Continued)*

	Reported subgroup analysis (Y/N): N
Participants	Country: United States Age (mean ± SD, range): 64.8 ± 10.8 years in the sodium hyaluronate group; 52.3 ± 16.4 years in the polyvinyl alcohol group Gender: 3 men and 17 women in the sodium hyaluronate group; 1 man and 14 women in the polyvinyl alcohol group Inclusion criteria: moderately severe keratoconjunctivitis sicca Exclusion criteria: not reported Equivalence of baseline characteristics (Y/N): N (age)
Interventions	Intervention #1: 0.1% sodium hyaluronate (Pharmacia) 8 times daily Intervention #2: 1.4% polyvinyl alcohol with chlorobutanol as a preservative (Liquifilm, Allergan Pharmaceuticals) 8 times daily Length of follow-up: 8 weeks Notes: eye drops was applied 8 times daily, but more frequent application was permitted; participants were asked to abstain from using eye drops 2 hours prior to examination
Outcomes	Primary outcome(s): subjective symptoms of dry eye; tear film osmolarity; TBUT; conjunctival staining with rose bengal; Schirmer's test; ocular surface impression cytology Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 1, 4 and 8 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: "The authors have no commercial interest in either of the products compared in this study" Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-masked" trial, but details of masking were not reported

Nelson 1988 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	1/38 (2.8%) dropped out, and was not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Pinto-Bonilla 2015

Methods	Study design: randomized, cross-over, controlled trial Study center: single center Number randomized (total and per group): 17 participants total: 9 participants into the Thealoz Duo first group; 8 participants into the Systane first group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: none Number analyzed: 17 participants total: 9 in the Thealoz Duo first group; 8 in the Systane first group Unit of analysis (individual or eye): individual Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Spain Age (mean ± SD, range): 49.3 ± 13.5, 33 to 70 years total: 45.3 ± 11.8, 33 to 70 years in the Thealoz Duo first group; 53.8±14.6, 33-70 years in the Systane first group Gender: 4 male and 13 female total: 3 male and 6 female the Thealoz Duo first group; 1 male and 7 female in the Systane first group Inclusion criteria: 1) men or women between 18 and 70 years of age with a diagnosis of moderate-to-severe dry eye syndrome (OSDI > 25) having used tear substitutes in the last 3 months; 2) willingness to give informed consent and to comply with the study protocol Exclusion criteria: 1) best distance corrected visual acuity less than 1/10; 2) severe blepharitis; 3) dry eye secondary to eyelid malposition, corneal dystrophy; 4) ocular neoplasia; 5) filamentous keratitis; 6) corneal neovascularization or orbital radiotherapy; 7) history of ocular disease including traumatism, infection, inflammation, allergy, or herpes within the last 3 months; 8) history of inflammatory corneal ulcer or uveitis within the last 12 months; 9) hypersensitivity to any component of the investigative substances; 10) allergic rhinitis that was current or susceptible to reactivation during the study; 10) any other medical or surgical history, disorder, or disease that might require modification of ongoing medication during the clinical investigation Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: trehalose and hyaluronic acid (Thealoz Duo®, Laboratoires Théa), five times daily

Pinto-Bonilla 2015 *(Continued)*

	Intervention #2: hydroxypropyl guar, polyethylene glycol and propylene glycol, and polyquaternium-1 preservative (Systane®, Alcon Inc.), five times daily Length of follow-up: 19 days Notes: both treatments administered as one drop five times daily in both eyes for 7 days, followed by a washout period of 5 days, then patients switched to the alternate treatment for 5 days
Outcomes	Primary outcome(s): patient satisfaction Secondary outcome(s): OSDI score, dry eye symptoms, ocular staining score, ocular clinical signs, Schirmer test, TBUT, global efficacy Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and days 7, 12 and 19 Other issues with outcome assessment (e.g., quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "The study was sponsored by Laboratoires Théa. The manuscript was prepared with the assistance of Dr JF Stolz, who was remunerated by Laboratoires Théa." Conflicts of interest: "The authors report no conflicts of interest in this work." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The two treatments were presented in different 10 mL bottles. As the bottle design is an integral part of the product conventional treatment, blinding was not possible."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of outcome assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This study was funded by a pharmaceutical company; authors were affiliated with a industry

Simmons 2004a

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: not reported
	Number randomized (total and per group): not reported
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: not reported
	Losses to follow-up: not reported
	Number analyzed: 73 participants
	Unit of analysis (individual or eye): not reported
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: Australia
	Age (mean ± SD, range): not reported
	Gender: not reported
	Inclusion criteria: moderate to severe dry eye
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1: 0.5% carboxymethyl cellulose (Refresh Plus® / Cellufresh®, Allergan) every 2 - 4 hours up to 12 times daily
	Intervention #2: 0.3% hydroxypropyl methylcellulose with bicarbonate (Bion Tears®, Alcon) every 2 - 4 hours up to 12 times daily
	Intervention #3: 0.2% carbomer 980 gel (Viscotears Gel®, Ciba Vision) every 2 - 4 hours up to 12 times daily
	Intervention #4: 0.3% hydroxypropyl methylcellulose (Polytears Free®, Alcon) every 2 - 4 hours up to 12 times daily
	Length of follow-up: 3 months
	Notes: there was a washout period of 14 days with a standard treatment
Outcomes	Primary outcome(s): frequency of artificial tear use
	Secondary outcome(s): not reported
	Adverse events reported (Y/N): N
	Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 1, 2, 4, 8, and 12
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: not reported
	Funding source(s): "This study was supported by Allergan Australia Pty Ltd."
	Conflicts of interest: not reported

Simmons 2004a *(Continued)*

	Publication language: English
	Notes: this trial was published in abstract form only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomized into each group were not reported; numbers who were withdrawn or lost to follow-up in each group were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial was funded by a pharmaceutical company; this trial was published in abstract form only

Simmons 2007

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: multicenter (5 sites)
	Number randomized (total and per group): 103 participants total; 50 into the CMC 0.5% group; 53 into the CMC 1.0% group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization or losses to follow-up: 4 participants in total (reasons and groups not reported)
	Number analyzed: 103 participants in total; 50 in the CMC 0.5% group; 53 in the CMC 1.0% group
	Unit of analysis (individual or eye): individual
	Reported power calculation (Y/N): N
	Reported subgroup analysis (Y/N): N
Participants	Country: United States
	Age (mean ± SD, range): not reported

Simmons 2007 *(Continued)*

	Gender: 27 men and 76 women Inclusion criteria: 1) mild to moderate dry eye defined as Schirmer's test without anesthesia between 5 and 15 mm in 5 minutes and the sum of corneal and interpalpebral conjunctival fluorescein staining scores between 2 and 33, as measured by a modified Oxford Scheme of staining Exclusion criteria: not reported Equivalence of baseline characteristics (Y/N): not reported
Interventions	Intervention #1 (CMC 0.5% group): 0.5% carboxymethylcellulose sodium with Purite as preservative (Refresh Tears, Allergan) 4 times daily Intervention #2 (CMC 1.0% group): 1% carboxymethylcellulose sodium with Purite as preservative (Refresh Liquigel, Allergan) 4 times daily Length of follow-up: 30 days Notes: there was a run-in period of 2 weeks with a low-viscosity artificial tear (0.2% hydroxypropyl methylcellulose with benzalkonium chloride as preservative)
Outcomes	Primary outcome(s): corneal and interpalpebral conjunctival staining Secondary outcome(s): questionnaire on symptoms, visual functions, and response to environmental triggers of ocular discomfort; acceptability; preference; BCVA; slit-lamp findings Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, days 7 and 30 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: authors were affiliated with a pharmaceutical company Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"masked" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"masked" trial, but details of masking were not reported

Simmons 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	4/103 (3.9%) did not complete trial
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Authors were affiliated with a pharmaceutical company

Simmons 2015a

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (13 sites) Number randomized (total and per group): 315 participants total; 105 to LT UD group; 103 to AqT UD group; 51 to LT MD group; 56 to AqT MD group Unit of randomization (individual or eye): individual Exclusions after randomization: 2 due to protocol violation (one AqT UD and one LT MD) Losses to follow-up: 3 participants due to adverse events (one LT UD, one LT MD, and one AqT MD) Number analyzed: 315 participants total; 105 to LT UD group; 103 to AqT UD group; 51 to LT MD group; 56 to AqT MD group in ITT analysis Unit of analysis (individual or eye): individual(worse eye) Reported power calculation (Y/N): Y (90% power) Reported subgroup analysis (Y/N): Y
Participants	Country: United States Age (mean ± SD, range): 54.4 ± 14.8, range 22 to 85 years in LT UD group; 55.8 ± 14.1, range 24 to 84 years in AqT UD group; 55.2 ± 14.5, range 23 to 81 years in LT MD group; 53.5 ± 13.9, range 22 to 83 years in AqT MD group Gender: 83 women (79.0%) in LT UD group; 87 women (84.5%) in AqT UD group; 44 women (86.3%) in LT MD group; 41 women (73.2%) in AqT MD group Inclusion criteria: 1) ≥ 18 years of age and in good general health; 2) OSDI score 18 to 65; 3) use of artificial tears at least twice daily, on average, for ≥3 months prior to baseline; 4) three consecutive measures of TBUT ≤ 10 seconds in at least one eye; 5) mild to moderate corneal or conjunctival staining, as indicated by grade ≥1 (modified NEI grid) staining, related to dry eye in at least one eye Exclusion criteria: 1) Schirmer's test (with anesthesia) ≤ 2 mm/5 minutes in either eye; 2) severe corneal or conjunctival staining, as indicated by grade 5 (modified NEI grid) staining, in either eye; 3) current use or use within 2 weeks of enrollment of topical ophthalmic medications such as corticosteroids, hypotensive agents, and generic cyclosporine was allowed if used ≥ 6 months prior to enrollment, or use of a systemic medication affecting dry eye; 4) wearing of contact lenses within 6 months prior to baseline; 5) active ocular infection, inflammation, allergy, or blepharitis; 6) abnormal corneal sensitivity, recent anterior segment surgery (eg, LASIK surgery or any surgery involving a limbal or corneal incision within 12 months of baseline visit) or trauma, anticipated or planned elective surgery during the study, or punctal occlusion Equivalence of baseline characteristics (Y/N): Y

Simmons 2015a *(Continued)*

Interventions	Intervention #1 (LT UD group): preservative-free unit-dose lipid tear formulation containing CMC, glycerin, polysorbate 80, boric acid, Pemulen™, erythritol, levocarnitine, castor oil (0.25%), sodium hydroxide, purified water (Refresh Optive® Advanced Sensitive) Intervention #2 (AqT UD group): preservative-free unit-dose aqueous tear formulation containing CMC, glycerin, boric acid, sodium borate, sodium citrate, potassium chloride, erythritol, levocarnitine, calcium chloride, magnesium chloride, sodium hydroxide, purified water (Refresh Optive® Sensitive) Intervention #3 (LT MD group): preserved multidose lipid tear formulation containing CMC, glycerin, polysorbate 80, boric acid, Pemulen™, erythritol, levocarnitine, castor oil (0.25%), Purite®, sodium hydroxide, purified water (Refresh Optive® Advanced) Intervention #4 (AqT MD group): preserved multidose aqueous tear formulation containing CMC, glycerin, boric acid, sodium borate, sodium citrate, potassium chloride, erythritol, levocarnitine, calcium chloride, magnesium chloride, Purite®, sodium hydroxide, purified water (Refresh Optive®) Length of follow-up: 30 days Notes: participants were allowed to use the assigned treatment as needed at least twice daily; use of adjunctive treatments (such as warm compression or eye lid cleansing) was allowed to continue during the course of the study, but any change in use (adding or stopping) was prohibited
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): TBUT; corneal staining with fluorescein; conjunctival staining with lissamine green; Schirmer's test with anesthesia; acceptability Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and days 7 and 30 Other issues with outcome assessment (e.g., quality control for outcomes if any): none
Notes	Study dates: October 2011 to February 2012 Trial registration: NCT01459588 Funding source(s): "This study was sponsored by Allergan, Inc., Irvine, CA, USA." Conflicts of interest: "The authors are employees of Allergan, Inc. The formulations used in the study are investigational or marketed products of Allergan, Inc. Writing and editorial assistance was provided to the authors by Sarah Whitfield, of Evidence Scientific Solutions, Philadelphia, PA, USA, and funded by Allergan, Inc. All authors met the International Committee of Medical Journal Editors authorship criteria. Neither honoraria nor payments were made for authorship." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated randomization scheme" was used
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"subject-masked and investigator-masked" study; "LT UD and AqT UD were supplied in identical 0.4 mL unit-dose vials, and LT MD and AqT MD were supplied in identical 15 mL multidose bottles"

Simmons 2015a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" study, but details about masking of outcome assessors were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The intent-to-treat population consisted of all randomized subjects and was used for all efficacy analyses"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the paper
Other bias	Unclear risk	This study was funded by a pharmaceutical industry; authors were affiliated with a industry

Simmons 2015b

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (22 sites) Number randomized (total and per group): 305 total; 101 to intervention #1; 100 to intervention #2; 104 to intervention #3 Unit of randomization (individual or eye): individual Exclusions after randomization: 8 participants total; 3 (due to adverse events) in intervention #2; 5 (3 adverse events; 2 lack of efficacy) in intervention #3 Losses to follow-up: 11 participants total; 4 (1 personal reasons; 3 other reasons) in intervention #1; 3 (2 personal reasons; 1 other reasons) in intervention #2; 4 (2 personal reasons; 2 other reasons) in intervention #3 Number analyzed: 264 participants total; 87 in intervention #1; 87 in intervention #2; 90 in intervention #3 in per protocol population Unit of analysis (individual or eye): individual Reported power calculation (Y/N): Y (80% power) Reported subgroup analysis (Y/N): N
Participants	Country: Australia; Canada Age (mean ± SD, range): 59.6 ± 14.5, 19 to 90 years in intervention #1; 59.2 ± 16.3, 19 to 85 years in intervention #2; 60 ± 13.3, 19 to 85 years in intervention #3 Gender: 23 men and 78 women in intervention #1; 20 men and 80 women in intervention #2; 14 men and 90 women in intervention #3 Inclusion criteria: 1) ≥18 years of age and in general good health; 2) OSDI score between 18 and 65 inclusive; 3) used artificial tears at least twice daily for ≥3 months prior to baseline; 4) three consecutive TBUT test results of ≤10 seconds in ≥1 eye; 5) grade 1 or greater corneal or conjunctival staining related to dry eye in ≥1 eye; 6) distance and high-contrast near visual acuity of 20/32 or better Exclusion criteria: 1) Schirmer's test score (with anesthesia) of ≤2 mm/5 min at baseline; 2) grade 5 corneal or conjunctival staining in either eye at baseline; 3) history of anterior segment surgery that could affect corneal sensitivity within 12 months prior to baseline; 4) use of topical ophthalmic medication during study or within 2 weeks prior to baseline, other than artificial tears; 5) use of topical cyclosporine within 3 months prior to baseline; 6) use of systemic medication that could affect vision or dry eye, including essential fatty acids, unless dose constant for ≥3 months and not expected to change

Simmons 2015b *(Continued)*

	during the study; 7) punctal occlusion with temporary plugs <30 days prior to baseline or with permanent plugs <3 months prior to baseline; 8) use of contact lenses within 6 months prior to baseline or anticipated use during the study; 9) uncontrolled systemic disease Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: CMC 0.5% and hyaluronic acid 0.1% (Optive Fusion, Allergan Inc.) Intervention #2: CMC 0.5% and hyaluronic acid 0.15% Intervention #3: CMC 0.5%, salts, and with stabilized oxychloro complex (SOC) (Refresh tears, Allergan, Inc.) Length of follow-up: 3 months Notes: participants were instructed to administer the assigned eye drops in both eyes as needed but at least twice daily
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): visual analog symptom scale; near visual acuity; TBUT; corneal staining; conjunctival staining; Schirmer's test; biomicroscopy Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and days 7, 30, 60 and 90 Other issues with outcome assessment (e.g., quality control for outcomes if any): none
Notes	Study dates: May 2011 to September 2012 Trial registration: NCT01294384 Funding source(s): “This study was sponsored by Allergan, Inc., Irvine, CA, USA.” Conflicts of interest: “The authors are employees of Allergan, Inc., Irvine, CA, USA. The formulations used in this study are investigational or marketed products of Allergan, Inc. The authors report no other conflicts of interest” Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“a computer-generated random allocation scheme” was used
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	”double-masked” trial; “To maintain subject and investigator masking, the artificial tears were provided in virtually identical 15-mL bottles and cartons; labels were nonbranded and did not list ingredients”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“double-masked” trial, but details about masking of outcome assessors were not reported
Incomplete outcome data (attrition bias)	Low risk	“The primary efficacy analysis used the ITT population of all randomized subjects and last observation carried forward (LOCF) for missing values. Sensitiv-

Simmons 2015b *(Continued)*

All outcomes		ity analyses used observed values in the per-protocol (PP) population of randomized subjects with no major protocol violations"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the paper
Other bias	Unclear risk	This study was funded by a pharmaceutical company; authors were affiliated with a industry

Sullivan 1997

Methods	Study design: randomized, parallel-group, controlled trial Study center: multicenter (7 sites) Number randomized (total and per group): 123 participants total; 62 into the carbomer gel group; 61 into the placebo group Unit of randomization (individual or eye): individual Exclusions after randomization: 16 participants in total; 6 (2 due to inefficacy of the treatment, 4 due to adverse events) in the carbomer group; 10 (8 due to inefficacy of the treatment, 2 due to adverse events) in the placebo group Losses to follow-up: 14 participants in total; 5 in the carbomer gel group; 9 in the placebo group Number analyzed:123 total, 62 in the carbomer group, and 61 in the placebo group at baseline; 118 total, 61 in the carbomer group, and 57 in the placebo group at day 10; 105 total, 54 in the carbomer group, and 51 in the placebo group at day 21; 97 total, 53 in the carbomer group, and 44 in the placebo group at day 42; 94 total, 51 in the carbomer group, and 43 in the placebo group at day 56 Unit of analysis (individual or eye): individual (worst eye) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): Y (disease severity at baseline)
Participants	Country: Australia; Austria; Belgium; France; Italy; United Kingdom Age (mean ± SD, range): 60.35 ± 12.75 years, range 22 to 85 years total; 59.69 ± 10.94, range 31 to 80 years in the carbomer group; 61.02 ± 14.42 years, range 22 to 85 years in the placebo group Gender: 15 men and 47 women in the carbomer group; 5 men and 56 women in the placebo group Inclusion criteria: 1) moderate to severe dry eye defined as positive rose bengal staining totaling at least 4 of 9 in at least 1 eye, and symptoms of foreign body sensation and discomfort of at least 1 of 3 Exclusion criteria: 1) active ocular infection or inflammation disease not related to dry eye; 2) corneal ulceration within the past 3 months; 3) progressive retinal disease; 4) wearing of contact lens; 5) ocular surgery within the past 3 months; 6) glaucoma or ocular hypertension; 7) cataract causing visual acuity to be 20/60 or worse; 8) recurrent corneal erosion syndrome; 9) eyelid or eyelash abnormalities; 10) monocular patients; 11) abnormalities of the nasolacrimal drainage apparatus Equivalence of baseline characteristics (Y/N): N (gender)
Interventions	Intervention #1: 0.3% carbomer ophthalmic gel 940 with 0.0008% benzalkonium chloride as preservative (Carbopol 934P, Alcon) 4 times daily up to 6 times Intervention #2: placebo (mannitol solution with 0.0008% benzalkonium chloride as preservative; vehicle of the carbomer ophthalmic gel) 4 times daily up to 6 times

Sullivan 1997 *(Continued)*

	Length of follow-up: 56 days Notes: there was a washout period of 1 to 7 days with preservative free saline; participants who required instillations > 6 times per day were withdrawn from trial and considered as treatment failure
Outcomes	Primary outcome(s): discomfort; dryness; foreign body sensation; rose bengal staining Secondary outcome(s): tearing; photophobia; erythema and swelling of eyelids; scaling of lid margins; conjunctival discharge; injection of the bulbar and palpebral conjunctiva; corneal filaments; corneal fluorescein staining; itching Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, days 10, 21, 42 and 56 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): "The authors thank Alcon Laboratories for supplying the clinical trial stock" Conflicts of interest: not reported Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"single-masked" trial; "patients were provided with masked medication by the trial coordinator."; "The participating ophthalmologists were not masked as to treatment but were requested not to ask the patients which medication they were using, unless an adverse event had been recorded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"single-masked" trial; "The participating ophthalmologists were not masked as to treatment but were requested not to ask the patients which medication they were using, unless an adverse event had been recorded."
Incomplete outcome data (attrition bias) All outcomes	High risk	"The intent-to-treat data set was used in this analysis"; "Patients (n=10) who discontinued due to treatment failure or who did not return after the baseline visit (n=6) had their last visit carried forward to all remaining scheduled visits for the purpose of analysis"; 9/62 (14.5%) in the carbomer gel group and 18/61 (29.5%) in the placebo group were not included in the analysis of dry/sandy sensation;11/62 (17.7%) in the carbomer gel group and 18/61 (29.5%) in the placebo group were not included in the analysis of dryness
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	A pharmaceutical firm provided clinical trial stock; participants who required instillations > 6 times per day were withdrawn from trial and considered as treatment failure; baseline characteristics were not equivalent

Tomlinson 2013

Methods	Study design: randomized, cross-over, controlled trial
	Study center: single center
	Number randomized (total and per group): 19 participants total
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: none
	Losses to follow-up: 1 participant
	Number analyzed: 18 participants total
	Unit of analysis (individual or eye): individual
	Reported power calculation (Y/N): Y
	Reported subgroup analysis (Y/N): N
Participants	Country: United Kingdom
	Age (mean ± SD, range): 41 ± 14 years
	Gender: 7 men and 11 women
	Inclusion criteria: 1) TBUT of < 10 secs using a Hir-Cal grid; 2) Schirmer's test of < 10 mm/5 without anesthesia in order to include mild dry eye cases 3) a grade of 1, 2 or 5 using the grading scale of Thai et al for thin-film interferometry and a score of ≥ 10 on the OSDI Questionnaire
	Exclusion criteria: not reported
	Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1: 0.5% carboxymethylcellulose sodium (Refresh Tears® Lubricant Eye Drops, Allergan) 3 times daily
	Intervention #2: 0.5% carboxymethylcellulose sodium plus castor oil(Optive Plus™ Lubricant Eye Drops, Allergan) 3 times daily
	Intervention #3: 1.0% glycerine plus castor oil(Refresh Ultra® Lubricant Eye Drops, Allergan) 3 times daily
	Length of follow-up: 2 weeks in each phase
	Notes: a minimum 1-week washout between each phase; drops were not allowed to be used for at least 1 hour before testing
Outcomes	Primary outcome(s): tear film evaporation; interferometry; TBUT; osmolarity; OSDI
	Secondary outcome(s): not distinguished
	Adverse events reported (Y/N): N
	Measurements taken, specify intervals at which outcomes assessed: baseline and week 2 in each phase
	Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported
	Trial registration: not reported

Tomlinson 2013 *(Continued)*

Funding source(s): "This work was supported by an unrestricted research grant to Professor Tomlinson from Allergan LLC."

Conflicts of interest: not reported

Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" trial, but details of masking were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind" trial, but details of masking were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	1/19 (5.3%) participant was lost to follow-up, and the was not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	This trial included both dry eye and non-dry eye participants; this trial was a cross-over design, and results were not separately reported by phases; this trial was funded by a pharmaceutical company

Waduthantri 2012

Methods	Study design: randomized, parallel-group, controlled trial
	Study center: single center
	Number randomized (total and per group): 30 participants total; 15 participants each group
	Unit of randomization (individual or eye): individual
	Exclusions after randomization: none
	Losses to follow-up: none
	Number analyzed: 30 participants in total; 15 participants each group
	Unit of analysis (individual or eye): individual (results on both eyes were reported separately)
	Reported power calculation (Y/N): Y, power of 80%
	Reported subgroup analysis (Y/N): N

Waduthantri 2012 *(Continued)*

Participants	Country: Singapore Age (mean ± SD, range): 55.9 ± 5.3 years in the Systane group; 54.7 ± 5.8 years in the Refresh group Gender: 3 men and 12 women in the Systane group; 1 man and 14 women in the Refresh group Inclusion criteria: 1) age between 40 and 65 years; 2) corneal fluorescein staining present in at least 1 of the 5 sectors in at least 1 eye; 3) at least 1 of the 6 dry eye symptoms (dryness, grittiness, redness, watering, crusting of lids, and sticking of lids together) based on the Salisbury Eye Evaluation study, must be present often or all the time; 4) TBUT of ≤ 5 secs or a Schirmer's result of < 8 mm in at least 1 eye and Yamaguchi score of 2 in at least 1 sector of 1 of the 4 lids; 5) ability to abstain from non-trial topical ophthalmic drops for 6 weeks. Exclusion criteria: 1) a known history of systemic conditions such as thyroid disorders, Sjogren syndrome, and rheumatoid arthritis; 2) ocular surface diseases such as pterygium; 3) obvious lid/orbital disease with lagophthalmos; 4) previously been treated with punctal plugs or punctum cautery; 5) wearing contact lenses or felt the necessity to wear contact lens throughout the duration of the study; 6) ocular surgery within the past 6 months; 7) LASIK within the past 1 year; 8) intake of central nervous system or hormonal drugs within past 30 days; 9) inability to withhold such drugs for at least 6 weeks; 10) use of nonlubricant ophthalmic drops within the past 30 days Equivalence of baseline characteristics (Y/N): N (severity of fluorescein staining in the left nasal and inferior zones)
Interventions	Intervention #1: 0.4% polyethylene glycol 400, 0.3% propylene glycol, and hydroxypropyl guar as gelling agent (Systane® Ultra, Alcon Laboratories) 4 times daily Intervention #2: 0.5% carboxymethylcellulose sodium (Refresh Tears®, Allergan) 4 times daily Length of follow-up: 6 weeks Notes: all participants underwent a 7-day washout period with saline eye drops
Outcomes	Primary outcome(s): SANDE score Secondary outcome(s): corneal fluorescein staining; TBUT; Schirmer's test Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, and weeks 1, 3, and 6 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: NCT00796926 Funding source(s): "This work was supported by grants NMRC/1206/2009, NMRC/0808/ 2003, NMRC/CPG/002/2003, NMRC/0982/2005, and NMRC/1206/ 2009 from National Medical Research Council (NMRC), Singapore, and Alcon Inc. (Alcon Inc. Funder) provided funding for consumables and study medication." Conflicts of interest: none Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A simple randomization process of picking the participants for each group from 30 blinded stubs was used."

Waduthantri 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-masked" trial; "Both study examiners and patients were masked to the type of treatment received by each patient. Masking was done by putting the bottles in a paper bag and removing the commercial labels."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked" trial; "Both study examiners and patients were masked to the type of treatment received by each patient. Masking was done by putting the bottles in a paper bag and removing the commercial labels."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	High risk	Some outcomes prespecified in protocol were not reported in the paper
Other bias	Unclear risk	This trial was funded by a pharmaceutical company; severity of fluorescein staining in the left nasal and inferior zones were not equivalent at baseline

Wang 2007

Methods	Study design: 3-arm randomized, parallel-group,controlled trial Study center: single center Number randomized (total and per group): 80 participants total ; 28 into the carbomer group; 26 into the hypromellose group; 26 into the lanolin group Unit of randomization (individual or eye): individual Exclusions after randomization: 13 participants in total due to protocol violation; 6 in the carbomer group; 3 in the hypromellose group; 4 in the lanolin group Losses to follow-up: none Number analyzed: 67 participants total; 22 in the carbomer group; 23 in the hypromellose group; 22 in the lanolin group Unit of analysis (individual or eye): individual (both eyes) Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: Taiwan Age (mean ± SD, range): 55.86 ± 15.66 years in the carbomer group; 50.08 ± 14.32 years in the cellulose group; 60.31 ± 11.21 years in the mineral oil group Gender: 3 men and 19 women in the carbomer group; 6 men and 17 women in the hypromellose group; 3 men and 19 women in the lanolin group Inclusion criteria: 1) 18 years of age or older; 2) dry eye defined as at least 1 of the following signs in both eyes: (a) Schirmer's test with anesthesia ≤ 5 mm/5 minutes in both eyes; (b) TBUT ≤ 10 secs; 3) dry eyes with grade II severity (i.e. symptoms with reversible signs) based on triple classification of dry eye

Wang 2007 *(Continued)*

	Exclusion criteria: 1) dry eye with grade III (symptoms with permanent signs) based on triple classification of dry eye; 2) systemic therapy such as beta blockers that could influence lacrimal secretion; 3) naso-lacrimal obstruction; 4) external eye disease inducing conjunctiva inflammation and/or infection and corneal scars; 5) wearing of contact lens; 6) any local treatment with eye drops and/or ointment other than for dry eye; 7) noncompliance with protocol; 8) Sjögren syndrome treated with oral steroids Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (carbomer group): 0.2% carbomer MW4,000,000 with 0.01% cetrimide as preservative (Vidisic Ophthalmic Gel, Dr. Gerhard Mann) 4 times daily Intervention #2 (hypromellose group): 0.32% hypromellose with 0.01% cetrimide as preservative (Artelac Ophthalmic Solution, Dr. Gerhard Mann) 4 times daily Intervention #3 (lanolin group): 0.3% anhydrous liquid lanolin with 0.05% methylparaben and 0.01% propylparaben as preservative(Duratears Ointment, Alcon) once daily Length of follow-up: 4 weeks Notes: there was a washout period of 1 month for participants using eye drops and/or ointment for dry eye
Outcomes	Primary outcome(s): symptoms; palpebral and bulber conjunctival injection; corneal fluorescein staining; Schirmer's test; TBUT; participant's subjective assessment of study treatment; local tolerability Secondary outcome(s): not distinguished Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2, and 4 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: between February 2003 and January 2005 Trial registration: not reported Funding source(s): not reported Conflicts of interest: none Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label" trial

Wang 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	"Thirteen patients were excluded as protocol deviations, leaving 67 patients for analysis in the ITT and safety populations. All protocol deviations consisted of ineligibility, off-window visits, et cetera."; although the authors said intention-to-treat analysis was followed, 13/80 (16.3%) participants who were randomized were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Wang 2010

Methods	Study design: randomized, parallel-group,controlled trial Study center: single center Number randomized (total and per group: 30 participants total; 15 per group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: none Number analyzed: 30 participants in total; 15 per group Unit of analysis (individual or eye): individual (both eyes) Reported power calculation (Y/N): Y (power not reported) Reported subgroup analysis (Y/N): N
Participants	Country: Taiwan Age (mean ± SD, range): 40.37 ± 14.96 years in the carbomer group; 49.49 ± 12.20 years in the HP-guar group Gender: 4 men and 11 women in the carbomer group; 6 men and 9 women in the HP-guar Inclusion criteria: 1) 20 years of age or older; 2) diagnosis of dry eye defined as impaired tear function and ocular surface abnormalities and having at least 1 of the following signs in both eyes: (a) Schirmer's test with anesthesia of ≤ 5 mm/5 minutes in both eyes on the day of recruitment; (b) TBUT of ≤ 10 secs Exclusion criteria: 1) known hypersensitivity to polyacrylic acid, cetrimide, polyethylene glycol, and propylene glycol; 2) systemic therapies that might induce corneal deposits or lacrimal secretion; 3) nasolacrimal obstruction; 4) external eye disease including conjunctival inflammation and/or infection, corneal scar, corneal dystrophy, and exophthalmos; 5) intraocular inflammation; 6) wearing of contact lens; 7) any local treatment with eye drops and/or ointment; 8) participation in another trial; 9) noncompliance with protocol; 10) Sjögrens syndrome Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (carbomer group): 0.2% carbomer-based lipid-containing gel with 0.01% cetrimide as preservative (Liposic® Ophthalmic Liquid Gel, Bausch & Lomb) 4 times daily Intervention #2 (HP-guar group): hydroxypropyl guar gel artificial tear with polyquaternium-1 as preservative (Systane® Lubricant Eye Drops, Alcon Laboratories, Inc) 4 times daily Length of follow-up: 4 weeks

Wang 2010 *(Continued)*

	Notes: participants were not allowed to use study medications 2 hours before the ophthalmic examination at study visits
Outcomes	Primary outcome(s): symptoms Secondary outcome(s): Schirmer's test; TBUT; objective signs (bulbar conjunctival redness, conjunctival foam (chemosis), conjunctival mucus threads, corneal epithelial filaments, and fluorescein staining of the cornea) Adverse events reported (Y/N): Y Measurements taken, specify intervals at which outcomes assessed: baseline, weeks 2, and 4 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: between August 2008 and January 2009 Trial registration: not reported Funding source(s): "Support for this study was provided by the institutional review board at Taipei Medical University Hospital (study number: CRC-03-08-03), Taipei Medical University Hospital Research (grant number: 97TMU-TMUH-10), and Taipei Medical University Research(grant number: TMU97-AE1-B13)." Conflicts of interest: "The authors have indicated that they have no other conflicts of interest regarding the content of this article." Publication language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized in balanced blocks with an equal probability of receiving either of the 2 treatments in the Department of Ophthalmology, Taipei Medical University Hospital"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" trial; "The study medications were not masked to the patients or the investigators"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label" trial; "The study medications were not masked to the patients or the investigators"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Xiao 2008

Methods	Study design: cluster-randomized controlled trial Study center: not reported Number randomized (total and per group): 60 participants total; 30 per group Unit of randomization (individual or eye): individual Exclusions after randomization: none Losses to follow-up: none Number analyzed: 120 eyes of 60 participants in total; 60 eyes of 30 participants per group Unit of analysis (individual or eye): eye Reported power calculation (Y/N): N Reported subgroup analysis (Y/N): N
Participants	Country: China Age (mean ± SD, range): 47.7 ± 2.3 years in the carbomer group; 46.6 ± 2.1 years in the CMC group Gender: 9 men and 51 women Inclusion criteria: 1) subjective symptom(s) (foreign body sensation, ocular dryness, burning, pain or photophobia); 2) at least 2 of the following objective signs; (a) Schirmer's test of < 10 mm/5 minutes; (b) TBUT < 10 secs; (c) positive corneal fluorescein staining Exclusion criteria: 1) not reported Equivalence of baseline characteristics (Y/N): Y
Interventions	Intervention #1 (carbomer group): 0.4% carbomer-based gel with 0.01% hexadecyl trimethyl ammonium bromide as preservative 3 to 4 times per day or more if needed Intervention #2 (CMC group): 1% carboxymethylcellulose sodium based artificial tear (Allergan Inc) 3 to 4 times per day or more if needed Length of follow-up: 3 months Notes: participants were allowed to use as many drops as needed
Outcomes	Primary outcome(s): subjective symptoms (ocular dryness, foreign body sensation, burning sensation, and pain); objective signs (Schirmer's test, TBUT, and corneal fluorescein staining) Secondary outcome(s): not distinguished Adverse events reported (Y/N): N Measurements taken, specify intervals at which outcomes assessed: baseline, and month 3 Other issues with outcome assessment (e.g. quality control for outcomes if any): none
Notes	Study dates: not reported Trial registration: not reported Funding source(s): not reported Conflicts of interest: not reported Publication language: English

Xiao 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"investigator-masked" trial, but details were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-masked" trial, but details were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	High risk	The unit of randomization (individual) was different from the unit of analysis (eye) and non-independence of eyes was not addressed in the analysis; participants were allowed to use as many drops as needed

BCVA: best-corrected visual acuity
LASIK: laser-assisted in situ keratomileusis
NEI: National Eye Institute
NITFBUT: noninvasive tear film break-up time
OSDI: ocular surface disease index
SANDE: symptom assessment in dry eye
secs: seconds
SESOD: subjective evaluation of symptoms of dryness
SS: Sjögren's syndrome
TBUT: tear break-up time

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amin 1996	Not a RCT
Bach 1972	Not participants of interest
Barsam 1972	Not a RCT
Caffery 1990	Not participants of interest
Calvão-Santos 2011	Not interventions of interest
Carlisle 2002	Intervention unclear

Study	Reason for exclusion
Chen 2011	Not interventions of interest
Christensen 2006	Overview of two RCTs
Christensen 2007	Overview of two RCTs
Christensen 2008	Overview of three previously published RCTs
Deschamps 1981	Not intervention of interest
Dumbleton 2008	Intervention unclear
Evangelista 2011	Not participants of interest
Fassihi 1989	Not a RCT
Feng 2006	Not participants of interest
Gensheimer 2012	Not interventions of interest
Gilbert 2008	Not intervention of interest
Graves 2003	Not a RCT; personal profile
Guillon 2013	Not participants of interest
Hartstein 2005	Not a RCT
Horn 2006	Short-term follow-up
Jacobi 2012	Not interventions of interest
Jones 1965	Not a RCT; review
Khanal 2008	Intervention unclear
Korb 2005a	Short-term follow-up
Korb 2005b	Not a RCT
Lekhanont 2014	Not interventions of interest
Lemp 1973a	Not a RCT; review
Lemp 1973b	Not a RCT; review
Leng 2013	Not interventions of interest
Limberg 1987	Not intervention of interest
Llamas-Moreno 2013	Not interventions of interest
Marquardt 1986	Not a RCT
Mayer 1994	Not a RCT

Study	Reason for exclusion
McCann 2012	Not intervention of interest
McDonald 2014	Not interventions of interest
Molemans 1982	Not intervention of interest
NCT00243711	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00347984	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00348322	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00348517	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00388791	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00493662	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00607776	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00620893	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00622037	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00724412	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT00840268	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01051804	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01061268	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01105910	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01160133	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01294956	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
NCT01368198	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)

Study	Reason for exclusion
NCT01741987	Clinical trial register record marked as completed with no study results posted and no publications provided (unpublished, no data available)
Nelson 1994	Not a RCT
Norn 1977	Short-term follow-up
Nursing Times 2006	Not a RCT
Otto 1996	Not a RCT
Prabhasawat 2015	Not participants of interest
Prather 2002	Overview of two studies
Pult 2012	Not interventions of interest
Rangwala 1981	Not a RCT
Ridder 2007	Not participants of interest
Rolando 2009	Not a RCT
Rozen 1998	Intervention unclear
Sanchez 2010	Not intervention of interest
Simmons 2002	Unclear: title only
Simmons 2004b	Short-tem follow-up
Smith 1993	Not intervention of interest
Solomon 1998	Not intervention of interest
Stein 2002	Unclear: title only
Tauber 2007	Not a RCT
Tian 2014	Not interventions of interest
Torkildsen 2006	Not intervention of interest
Utech 2004	Intervention unclear
Vehige 2003	Intervention unclear
Vehige 2005	Intervention unclear
Vehige 2009	Not participants of interest
Vicario-de-la-Torre 2007	Not a RCT; editorial
Villani 2011	Not intervention of interest

Study	Reason for exclusion
Watanabe 2012	Not a RCT
Wright 1987	Not intervention of interest

RCT: randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Amrane 2014

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 79 total; 44 in the Cationorm group; 35 in the Refresh group
Participants	Country: France Age (mean ± SD, range): 61.3 ± 15.4 years in the Cationorm group; 61.9 ± 12.5 years in the Refresh group Gender: 90.9% women in the Cationorm group; 80.0% in the Refresh group Inclusion criteria: men and women 18 years of age and over, who had given their written informed consent and whose dry eye disease had been under treatment for at least 3 months. The diagnosis of mild to moderate dry eye disease was validated by the presence of at least 2 of the following bilateral dry eye symptoms (score ≥ 1 on a 0 to 3-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe)): burning/stinging, eye dryness, itching, pain, sandy feeling/grittiness, sticky feeling, foreign-body sensation, photophobia; and the presence of at least 3 of the following 4 objective parameters in each eye: • mean TBUT ≤ 10 secs; • Schirmer's test without anesthesia ≤ 10 mm/5 minutes; • corneal fluorescein staining score > 1 (Oxford scale); • lissamine green staining total score ≥ 3 (Van Bijsterveld score) Exclusion criteria: • severe dry eye disease defined by the presence of at least 1 of the following criteria: need for at least 8 instillations/day of artificial tears, confluent superficial punctate keratitis > 2 (Oxford scale), conjunctival hyperemia with a score > 3 (McMonnies scale), moderate or severe blepharitis, conjunctival chemosis ≥ 2 on a 0 to 4-point scale; • ocular inflammation (Tyndall score > 0); • history of ocular allergy.
Interventions	Intervention #1: cationic emulsion (Cationorm) Intervention #2: polyvinyl alcohol and povidone (Refresh) Length of follow-up: 28 days
Outcomes	Primary outcome(s): TBUT; Schirmer's test; lissamine green staining; corneal fluorescein staining; oculopalpebral examination Secondary outcome(s): not distinguished

Amrane 2014 *(Continued)*

	Adverse events: yes
Notes	Study dates: unclear Study sponsor: Santen SAS Investigator: M Amrane (Santen SAS) Status: published August 2014, we have requested translation of the full-text report, which is in French

NCT00514852

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 316 total; 157 to intervention #1; 159 to intervention #2
Participants	Country: United States Age: not reported Gender: 37 men and 120 women in intervention #1; 34 men and 125 women in intervention #2 Inclusion criteria: mild, moderate or severe symptoms of dry eye Exclusion criteria: • "Uncontrolled systemic disease • Use of systemic medications affecting dry eye • Pregnancy or planning a pregnancy • Contact lens wear"
Interventions	Intervention #1: carboxymethylcellulose and glycerin-based artificial tear, 1 to 2 drops into each eye as needed but at least twice daily Intervention #2: carboxymethylcellulose (Refresh Plus), 1 to 2 drops into each eye as needed but at least twice daily Length of follow-up: 30 days
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): Schirmer's test; TBUT; Patient Acceptability Score (dryness); Patient Acceptability Score (vision); ocular surface (corneal) fluorescein staining; ocular surface (conjunctival) fluorescein staining; SESoD score Adverse events: yes
Notes	Study dates: October 2007 to January 2008 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT00544713

Methods	Study design: randomized, parallel-group, controlled trial

NCT00544713 *(Continued)*

	Number randomized (total and per group): 228 total; 114 each group
Participants	Country: United States Age: not reported Gender: 52 men and 62 women in intervention #1; 63 men and 51 women in intervention #2 Inclusion criteria: • "Candidate for bilateral LASIK surgery for myopia correction in the range of -1.00 to -8.00 diopters" Exclusion criteria: • "Dry eye signs and symptoms • Preoperative soft or rigid contact lens wear within last 7 or 30 days, respectively • Pregnancy or planning pregnancy • Uncontrolled systemic disease • Use of systemic medications affecting dry eye"
Interventions	Intervention #1: carboxymethylcellulose and glycerin-based artificial tear Intervention #2: carboxymethylcellulose (Refresh Plus®) Length of follow-up: 90 days
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): patient acceptability; BCVA; corneal topography; total higher order aberration (HOA); corneal staining with fluorescein; conjunctival staining with lissamine green; TBUT; study product usage Adverse events: yes
Notes	Study dates: September 2007 to June 2008 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT00756678

Methods	Study design: randomized, cross-over, controlled trial Number randomized: 51 participants
Participants	Country: United States Age: not reported Gender: 14 men and 37 women Inclusion criteria: • "Male or Female • At least 18 years of age • Current use of artificial tears"

NCT00756678 *(Continued)*

	Exclusion criteria: • "Any uncontrolled systemic disease • Pregnancy or planning a pregnancy • Contact lens wear"
Interventions	Intervention #1: carboxymethylcellulose and glycerin (Optive™), 1 drop in both eyes as needed Intervention #2: polyethylene glycol 400 (blink® Tears), 1 drop in both eyes as needed Length of follow-up: 7 days
Outcomes	Primary outcome(s): frequency of eye drop use Secondary outcome(s): Dry Eye Disease Comfort Assessment score; acceptability questionnaire; preference questionnaire Adverse events: yes
Notes	Study dates: September 2008 to August 2009 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT00761202

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 50 total; 22 to intervention #1; 28 to intervention #2
Participants	Country: United Kingdom Age: not reported Gender: 5 men and 16 women in intervention #1; 6 men and 20 women in intervention #2 Inclusion criteria: • "18 years or over • Contact lens wearer, spectacle wearer or non-spectacle wearer • Mild to severe dry eye symptoms, defined as OSDI score 13 to 100 • Mild to moderate conjunctival staining in each eye and/or mild to moderate corneal staining in each eye • Best corrected visual acuity of 6/9 in each eye" Exclusion criteria: • "Previously used Hylocomod or Optive eyedrops • Systemic allergy or eye allergy • Systemic disease which might have an ocular component and/or interfere with contact lens wear • Autoimmune disease which might have an ocular component and/or interfere with contact lens wear • Systemic medication which might have eye side effects and or interfere with contact lens wear • Eye infection or use of eye medication"

NCT00761202 *(Continued)*

Interventions	Intervention #1: sterile solution containing sodium carboxymethylcellulose and glycerin, preserved with PURITE® (Optive™) as required, but at least 3 times per day Intervention #2: sodium hyaluronate (Hylocomod) as required, but at least 3 times per day Length of follow-up: 1 month
Outcomes	Primary outcome(s): conjunctival staining by lissamine green Secondary outcome(s): corneal staining by fluorescein; conjunctival hyperemia; ocular comfort and ocular symptoms; daily eyedrop usage; lipid layer pattern assessment Adverse events: yes
Notes	Study dates: August 2007 to June 2008 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT00932477

Methods	Study design: randomized, cross-over, controlled trial Number randomized: 47 participants
Participants	Country: United States Age: not reported Gender: 5 men and 42 women Inclusion criteria: mild, moderate or severe symptoms of dry eye Exclusion criteria: • "Uncontrolled systemic disease • Contact lens wear • Participation in another clinical study"
Interventions	Intervention #1: carboxymethylcellulose sodium, glycerin and polysorbate 80-based artificial tear (formulation 1), 1 to 2 drops into each eye 3 times per day Intervention #2: carboxymethylcellulose sodium, glycerin and polysorbate 80-based artificial tear (formulation 2), 1 to 2 drops into each eye 3 times per day (formulation 2) Intervention #3: glycerin and polysorbate 80-based artificial tear (Refresh Dry Eye Therapy®), 1 to 2 drops into each eye 3 times per day Length of follow-up: 1 week
Outcomes	Primary outcome(s): tolerability questionnaire mean scores Secondary outcome(s): number of participants with at least 1 severity grade increase in biomicroscopy findings; BCVA Adverse events: yes

NCT00932477 *(Continued)*

Notes	Study dates: August 2009 to September 2009 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT00938704

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 70 total; 33 to intervention #1; 37 to intervention #2
Participants	Country: Germany Age: not reported Gender: 10 men and 23 women in intervention #1; 9 men and 28 women in intervention #2 Inclusion criteria: • "Current use of an artificial tear product at least 2 times per day (e.g. for relief of dry eye symptoms of dryness). • Be likely to complete the entire course of study and to comply with appropriate instructions" Exclusion criteria: • "Have undergone refractive surgery (e.g., cataract surgery, PRK, LASIK, or any surgery involving a limbal or corneal incision) within the last 12 months. • Have uncontrolled systemic disease • Are currently using, or have used within 14 days of study enrollment, any ocular medications other than artificial tears • Have anticipated contact lens wear during the study • Have an active ocular infection"
Interventions	Intervention #1: carboxymethylcellulose 0.5% + glycerin 0.9% (Optive™ Sensitive) as needed, but at least 1 drop 3 times a day Intervention #2: sodium hyaluronate 0.18% (Vismed®) as needed, but at least 1 drop 3 times a day Length of follow-up: 2 weeks
Outcomes	Primary outcome(s): OSDI Secondary outcome(s): TBUT; corneal staining; conjunctival staining (temporal and nasal) Adverse events: yes
Notes	Study dates: June 2009 to June 2009 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT01010282

Methods	Study design: 3-arm, randomized, parallel-group, controlled trial Number randomized (total and per group): 288 total; 97 to intervention #1; 95 to intervention #2; 96 to intervention #3
Participants	Country: United States Age: not reported Gender: 21 men and 76 women in intervention #1; 25 men and 70 women in intervention #2; 26 men and 70 women in intervention #3 Inclusion criteria: • "Current use of an artificial tear at least twice daily, for at least three months prior to Day 1, on average • Ability/agreement to wear habitual correction (glasses) during study period" Exclusion criteria: • "Known allergy or sensitivity to the study product(s) or its components • Anticipate contact lens wear during the study, or subject has worn contact lenses in the last six months • Chronic use of systemic medications which may affect a dry eye condition • Active ocular allergy or infection • Use of Restasis® or other topical cyclosporine products within 3 months prior to Day 1 • Current use of any topical ophthalmic medications, have used within 2 weeks prior to Day 1, or are likely to use during study."
Interventions	Intervention #1: carboxymethylcellulose sodium, glycerin and polysorbate 80-based artificial tear (formulation 1), 1 to 2 drops in each eye, as needed, but at least twice daily Intervention #2: carboxymethylcellulose sodium, glycerin and polysorbate 80-based artificial tear (formulation 2), 1 to 2 drops in each eye, as needed, but at least twice daily Intervention #3: glycerin and polysorbate 80-based artificial tear (Refresh Dry Eye Therapy® Lubricant Eye Drops), 1 to 2 drops in each eye, as needed, but at least twice daily Length of follow-up: 90 days
Outcomes	Primary outcome(s): SESoD score Secondary outcome(s): OSDI total score; TBUT; corneal staining; conjunctival staining severity score Adverse events: none reported
Notes	Study dates: November 2009 to April 2010 Study sponsor: Allergan Investigator: not reported Status: completed with results posted; no publications provided

NCT01688726

Methods	Study design: randomized, parallel-group, controlled trial

NCT01688726 *(Continued)*

	Number randomized (total and per group): 91 total; 46 to intervention #1; 45 to intervention #2
Participants	Country: not reported Age: not reported Gender: 16 men and 30 women in intervention #1; 16 men and 29 women in intervention #2 Inclusion criteria: • "Non-contact lens wearer; • Symptomatology as defined by the Ocular Surface Disease Index (OSDI) questionnaire; • Lipid deficiency; • Best visual acuity of 6/9 or better in each eye; • Willingness to adhere to the instructions set in the clinical protocol; • Signature of the subject informed consent form; • Other protocol-defined inclusion criteria may apply." Exclusion criteria: • "Use of systemic medication which might produce dry eye side effects; • Systemic disease which might produce dry eye side effects; • Active or recent ocular inflammation or infection; • Use of ocular medication; • Significant ocular anomaly; • Previous ocular surgery; • Previous use of Restasis; • Any medical condition that might be prejudicial to the study; • Pregnant or lactating; • Other protocol-defined exclusion criteria may apply."
Interventions	Intervention #1: Systane® Balance eyedrops, 1 drop 4 times a day Intervention #2: Minims® Saline 0.9% eyedrops, 1 drop 4 times a day Length of follow-up: 1 month
Outcomes	Primary outcome(s): bulbar conjunctival staining Secondary outcome(s): high contrast logMAR time controlled visual acuity; noninvasive TBUT Adverse events: yes
Notes	Study dates: December 2012 to November 2013 Study sponsor: Alcon Research Investigator: Michel Guillon, PhD, FCOptom, FAAO, CCTI (OTG Research & Consultancy) Status: completed with results posted; no publications provided

NCT01733732

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 54 total; 27 each group
Participants	Country: United States

NCT01733732 *(Continued)*

	Age: not reported Gender: 10 men and 17 women in intervention #1; 11 men and 16 women in intervention #2 Inclusion criteria: • "Read, sign, and date the Informed Consent Document; • Must not have used any topical ocular drops for approximately 24 hours prior to Visit 1; • Meet the protocol-specified dry eye criteria at Screening Visit (Visit 1); • Intraocular pressure (IOP) less than or equal to 22 millimeters of mercury (mmHg) in both eyes; • Other protocol-defined inclusion criteria may apply." Exclusion criteria: • "History or evidence of ocular or intraocular surgery or serious trauma in either eye within the past 6 months; • Current punctal occlusion of any type (e.g., collagen plugs, silicone plugs); • History or evidence of epithelial herpes simplex keratitis (dendritic keratitis); vaccinia; active or recent varicella viral disease of the cornea and/or conjunctiva; chronic bacterial disease of the cornea and/or conjunctiva and/or eyelids; mycobacterial infection of the eye; and/or fungal disease of the eye; • Use of any concomitant topical ocular medications during the study period; • Currently using Restasis but unwilling to discontinue its use 1 month prior to screening and for the entire study period; • Use of systemic medications that may contribute to dry eye unless on a stable dosing regimen for a minimum of 30 days prior to Visit 1 and that remains stable throughout the study; • Uncontrolled ocular conditions such as uveitis, glaucoma or any other ocular condition that may preclude the safe administration of either drop under investigation; • Other protocol-defined exclusion criteria may apply."
Interventions	Intervention #1: Systane® Balance Lubricant Eye Drops, 1 drop in each eye 4 times a day Intervention #2: Systane® Gel, 1 drop in each eye 4 times a day Length of follow-up: 30 days
Outcomes	Primary outcome(s): OSDI Secondary outcome(s): BCVA; slit-lamp assessment; meibomian gland expression; noninvasive keratographic TBUT; tear meniscus height; ocular surface staining; tear inflammatory cytokine expression; HLA-DR inflammatory biomarker expression; HLA-DR and TNF-alpha gene expression; Schirmer's test; intraocular pressure Adverse events: yes
Notes	Study dates: March 2013 to October 2013 Study sponsor: Alcon Research Investigator: Penny A Asbell, MD (Icahn School of Medicine at Mount Sinai) Status: completed with results posted; no publications provided

BCVA: best-corrected visual acuity
HLA-DR: human leukocyte antigen - antigen D related
LASIK: laser-assisted in situ keratomileusis
logMAR: logarithm of the minimum angle of resolution
OSDI: ocular surface disease index
SD: standard deviation
secs: seconds

SESoD: subjective evaluation of symptom of dryness
TBUT: tear break-up time
TNF: tumor necrosis factor

Characteristics of ongoing studies *[ordered by study ID]*

NCT01335126

Trial name or title	"Comparison of Tolerability and Clinical Performance of Two Emulsion-type Artificial Tears"
Methods	Study design: randomized, cross-over, controlled trial Number randomized: 48 (estimated)
Participants	Country: not reported Age: not reported Gender: both Inclusion criteria: • Aged ≥18 • Men or women • Participant is in generally good and stable overall health • Patient likely to comply with study guidelines and study visits • Informed consent signed • OSDI score > 18 or TBUT < 10 secs Exclusion criteria: • "Corneal refractive surgery or contact lens wear within 6 months of this study • Current use of Restasis • Intra-ocular surgery within 6 months or ocular laser surgery within 6 months • Pregnant or lactating women • Ocular pathology (includes glaucoma and cataract), which could impact results and/or place patient at risk"
Interventions	Intervention #1: emulsion type artificial tear Intervention #2: emulsion type artificial tear Length of follow-up: 8 weeks
Outcomes	Primary outcome(s): tolerability questionnaire Secondary outcome(s): acceptability questionnaire; TBUT Adverse events: none reported
Starting date	March 2011
Contact information	Study sponsor: Allergan Investigator: Milton M Hom, OD FAAO (private practice)
Notes	Status: enrolling participants by invitation only

NCT01382810

Trial name or title	"Altaire Gel Forming Solution Versus Refresh Tears for the Treatment of Dry Eye Signs and Symptoms"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 100 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Patients 18 years or older. • Males or females. • Patient reported dry eye symptoms (episodic, annoying, activity limiting). • Physician assessment of mild-moderate dry eye. • Patient willing to instill drops TID and complete entire length of protocol. • TBUT ≤ 10 seconds. • At least Grade 6 Corneal Staining." Exclusion criteria: • "Current topical cyclosporine use (Restasis) • Current Refresh use. • Refractive surgery within the last 6 months. • Oral or topical corticosteroid use. • Severe dry-eye patients by physician assessment. • Current active blepharitis. • Oral doxycycline use. • Oral antihistamine use."
Interventions	Intervention #1: Altaire Gel forming solution, 3 times daily Intervention #2: Refresh Tears, 3 times daily Length of follow-up: 2 months
Outcomes	Primary outcome(s): TBUT Secondary outcome(s): conjunctival and corneal staining Adverse events: none reported
Starting date	March 2011
Contact information	Study sponsor: Innovative Medical Investigator: Mitch Jackson, MD (Jackson Eye, SC) and Paul Koch, MD (Koch Eye Associates)
Notes	Status: recruitment status unknown; recruiting as of June 2012

NCT01384851

Trial name or title	"Efficacy of the Chronic Application of Tear Formulations"
Methods	Study design: 3-arm randomized, cross-over, controlled trial Number randomized: 38 (estimated)
Participants	Country: United Kingdom Age: not reported Gender: both Inclusion criteria: • "Be between the ages of 18 and 79 years of age. • Must understand and be able, willing and likely to fully comply with study procedures and restrictions." Exclusion criteria: • "Active ocular allergy • Current contact lens wear • Any topical ophthalmic drops within 1 week of initial screening visit. • Started or changed the dose of chronic systemic medication known to affect tear production including, but not limited to antihistamines, antidepressants, diuretics, corticosteroids or immunomodulators within 30 days of initial screening visit. • Systemic disease known to affect tear production or loss including, but not limited to thyroid eye disease, that has been diagnosed or has not been stable within 30 days initial of screening visit. • Known hypersensitivity to any of the agents used in testing."
Interventions	Intervention #1: Next Generation Emulsion Multi-Dose Eye Drop (9963X), 1 drop both eyes 4 times daily Intervention #2: Refresh Dry Eye Therapy® Lubricant Eye Drops, 1 drop both eyes 4 times daily Intervention #3: Refresh Contacts, 1 drop both eyes 4 times daily Length of follow-up: 2 weeks
Outcomes	Primary outcome(s): tear film evaporation Secondary outcome(s): interferometry; tear film osmolarity; TBUT; tear sampling and biomarker analysis Adverse events: none reported
Starting date	July 2011
Contact information	Study sponsor: Glasgow Caledonian University; Allergan Investigator: Alan Tomlinson, DSc, PhD (Glasgow Caledonian University)
Notes	Status: recruitment status unknown; not yet recruiting as of February 2011

NCT01664949

Trial name or title	"A Study to Compare the Safety and Efficacy of A New Eye Drop Formulation With OPTIVE™ in Subjects With Dry Eye Disease"

NCT01664949 *(Continued)*

Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 460 total; 224 to intervention #1; 236 to intervention #2
Participants	Country: Australia; Belgium; France; Germany; Italy; Russian Federation; Spain; United Kingdom Age: not reported Gender: 42 men and 182 women in intervention #1; 47 men and 189 women in the intervention #2 Inclusion criteria: • "Have used artificial tears for dry eye" Exclusion criteria: • "Start date of over the counter, herbal, prescription or nutritional supplements that may affect dry eye or vision within 3 months prior to study start or an anticipated change in dosage during the study • History of eye surgery or trauma in the 6 months prior to study start • Current use or use within 2 weeks of study start, of topical eye medications."
Interventions	Intervention #1: carboxymethylcellulose-based eye drop formulation A, 1 to 2 drops in each eye as needed at least twice daily Intervention #2: carboxymethylcellulose-based preservative-free lubricant eye drops (OPTIVE™), 1 to 2 drops in each eye as needed at least twice daily Length of follow-up: 90 days
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): TBUT; corneal staining; conjunctival staining; Schirmer's test Adverse events: yes
Starting date	January 2013
Contact information	Study sponsor: Allergan Investigator: not reported
Notes	Status: completed May 2014

NCT01863368

Trial name or title	"Clinical Evaluation of Systane® ULTRA Compared to OPTIVE® in Ocular Surface Staining"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized (total and per group): 94 total; 46 to intervention #1; 48 to intervention #2
Participants	Country: France; Germany Age (mean ± SD, range): 63.5 ± 13.1 years in intervention #1; 65.2 ± 14.3 years in intervention #2 Gender: 7 men and 39 women in intervention #1; 8 men and 40 women in intervention #2 Inclusion criteria:

NCT01863368 *(Continued)*

	• "Willing and able to attend all study visits. • Diagnosis of dry eye, as specified in protocol. • Uses artificial tears, as specified in protocol. • Other protocol-defined inclusion criteria may apply." Exclusion criteria: • "Poor visual acuity, as specified in protocol. • Women of childbearing potential who are pregnant, lactating, or not using adequate birth control, as specified in protocol. • Any hypersensitivity or allergy to the investigational products or ingredients. • Any eye disorder, ocular surgery, medication, medical condition, or systemic disease, as specified in protocol. • Contact lens use within 2 weeks of Screening Visit. • Other protocol-defined exclusion criteria may apply."
Interventions	Intervention #1: Systane® ULTRA lubricant eyedrops, 1 drop in each eye 4 times a day for 35 days (Phase I), followed by 55 days additional use as needed (Phase II) Intervention #2: OPTIVE® lubricating eyedrops, 1 drop in each eye 4 times a day for 35 days (Phase I), followed by 55 days additional use as needed (Phase II) Length of follow-up: 35 days (Phase I), and 55 days (Phase II)
Outcomes	Primary outcome(s): TOSS Score Secondary outcome(s): OSDI score; IDEEL treatment effectiveness score; IDEEL treatment inconvenience score Adverse events: yes
Starting date	September 2013
Contact information	Study sponsor: Alcon Research Investigator: Steve Burmaster (Alcon Research)
Notes	Status: completed June 2014

NCT01959854

Trial name or title	"Efficacy of Topical 0.2% Xanthan Gum in Patients With Dry Eye"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 30 (estimated)
Participants	Country: Italy Age: not reported Gender: both Inclusion criteria: • age 60 years and older • OSDI between 12 and 23

NCT01959854 *(Continued)*

	Exclusion criteria: • "contact lens wear and use of other ophthalmic solutions with the exception of artificial tears"
Interventions	Intervention #1: 0.25% carboxymethylcellulose preservative-free, 1 drop in each eye 4 times a day Intervention #2: 0.2% xanthan gum preservative-free, 1 drop in each eye 4 times a day Length of follow-up: 30 days
Outcomes	Primary outcome(s): OSDI Secondary outcome(s): visual analog rating scale; fluorescein staining Adverse events: none reported
Starting date	September 2013
Contact information	Study sponsor: SIFI SpA Investigator: Pasquale Aragona, MD (University of Messina)
Notes	Status: completed October 2014

NCT01967147

Trial name or title	"Clinical Outcomes Following Treatment With Systane® Balance in Dry Eye Subjects"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 278 (estimated)

Participants	Country: United States
	Age: not reported
	Gender: both
	Inclusion criteria:
	• "Must have all of the following in at least 1 eye at Screening:
	  ◦ Meibomian Gland Dysfunction (MGD) grading for Expressibility ≤ 2 and Meibum Quality ≤ 2,
	  ◦ The average of 3 measures of TFBUT < 5 seconds, and
	  ◦ Unanesthetized Schirmer I test of ≥ 3 mm.Must have an Ocular Surface Disease Index (OSDI) Score ≥ 18 at Visit 1 prior to randomization (ie, after 2 weeks of run-in with Preservative-Free 0.9% Saline administered 4 times a day).
	• Must have best-corrected visual acuity of 55 letters or better in each eye as assessed using an early treatment diabetic retinopathy study (ETDRS) chart (letter read method).
	• Physician diagnosis of dry eye at least 6 months prior to Screening visit.
	• Willing and able to attend all study visits.
	• Must sign a written informed consent form.
	• Other protocol-defined inclusion criteria may apply."
	Exclusion criteria:
	• "Subjects on topical ocular treatments containing benzalkonium chloride (BAK), or other products with known toxicity to the corneal surface, within 30 days of Screening.
	• Subjects who have started, stopped, or changed a lid hygiene regimen within 30 days of Screening.
	• Use of any artificial tears/lubricants/gels/rewetting drops within 4 hours of Screening.

NCT01967147 *(Continued)*

	• Women of childbearing potential are excluded from participating in this study if they meet any of the following conditions:"
	  ○ Currently pregnant, or
	  ○ Test positive for pregnancy at Screening visit, or
	  ○ Currently breast feeding, or
	  ○ Are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study.
	• Hypersensitivity to the use of any of the study products or allergy to any ingredient in the study products.
	• Has an active ocular allergy.
	• Any ocular abnormalities that could adversely affect the safety or efficacy outcome, including eyelid anomalies, corneal disorders, history of herpes simplex, etc.
	• Subjects taking any systemic medication known to cause dry eye unless they have been on stable therapy/dosage for at least 30 days prior to Screening and will remain on a stable dosage for the duration of the study.
	• History of any ocular or intraocular surgery (including periocular Botox injections), eyelid surgery, keratorefractive procedure, corneal transplant and its variants, or serious ocular trauma within 1 year of Screening.
	• Active ocular infection (bacterial, viral or fungal), active inflammation not associated with dry eye such as uveitis, iritis, active blepharitis, active allergic conjunctivitis, etc.
	• Subjects with punctal plug insertion or diathermy procedure initiated within 30 days of Screening.
	• Any significant illnesses that could be expected to interfere with the study parameters.
	• Subjects with active oculodermal rosacea with meibomian gland dysfunction.
	• Participation in an investigational drug or device trial within 30 days of Screening.
	• Contact lens use within 30 days prior to Screening, or unwilling to avoid contact lens use during the course of the study.
	• Unwilling to avoid the use of additional artificial tears/lubricants/gels/rewetting drops (other than the assigned study medication) throughout the course of the study.
	• Other protocol-defined exclusion criteria may apply."

Interventions	Intervention #1: propylene glycol, 0.6% eye drops, 1 drop in each eye, 4 times per day, during Phase I (day 0 - 35), followed by 1 drop in each eye as needed during Phase II (day 35 - 90) Intervention #2: preservative-free 0.9% saline solution, 1 drop in each eye, 4 times per day, during Phase I (day 0 - 35), followed by 1 drop in each eye as needed during Phase II (day 35 - 90) Length of follow-up: 35 to 90 days
Outcomes	Primary outcome(s): TBUT Secondary outcome(s): TOSS score; IDEEL treatment effectiveness score; IDEEL treatment inconvenience score Adverse events: not reported
Starting date	February 2014
Contact information	Study sponsor: Alcon Research Investigator: Christine Rosko (Alcon Research)
Notes	Status: completed January 2015

NCT02014922

Trial name or title	"A Study to Determine the Relief of Dry Eye Symptoms With the Use of TheraTears® Products (DUNLIN)"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 33 (estimated)
Participants	Country: Canada Age: not reported Gender: Not reported Inclusion criteria: • "Is between 18 and 65 years of age and has full legal capacity to volunteer; • Has read and signed an information consent letter; • Is willing and able to follow instructions and maintain the appointment schedule; • Exhibits symptoms of dry eye for at least 3 months; • Has an OSDI score of ≥ 23; • Is currently on a non-omega 3 dry eye treatment regimen that, at the minimum consists of instilling artificial tears at least once a day for the past 3 months; • Has an average non-invasive tear breakup time ≤ 5.00 seconds in at least one eye." Exclusion criteria: • "Is participating in any concurrent clinical or research study; • Has any known active* ocular disease and/or infection and/or allergies; * For the purposes of study, active ocular disease is defined as infection or inflammation which requires therapeutic treatment. Lid abnormalities (blepharitis, meibomian gland dysfunction, papillae), corneal and conjunctival staining and dry eye are typical findings and are not considered active ocular disease. Neovascularization and corneal scars are the result of previous hypoxia, infection or inflammation and are therefore not active. • Has a systemic condition that in the opinion of the investigator may affect a study outcome variable; • Is using any systemic or topical medications that in the opinion of the investigator may affect a study outcome variable; • Has known sensitivity to the diagnostic pharmaceuticals to be used in the study; • Is pregnant, lactating or planning a pregnancy at the time of enrollment, as determined verbally; • Is aphakic; • Has undergone refractive error surgery; • Has taken part in another (pharmaceutical) research study within the last 30 days; • Has worn contact lenses within the past 5 years; • Is currently using or have used omega 3 supplements in the past 3 months."
Interventions	Intervention #1: TheraTears® Lubricant Eye Drop Drug; TheraTears® preservative-free single-use containers Dietary Supplement; TheraTears® Nutrition Other; TheraTears® TheraLid® Eyelid Cleanser Intervention #2: control (habitual artificial tears, and/or additional habitual concurrent dry eye treatments) Length of follow-up: 3 months
Outcomes	Primary outcome(s): OSDI score; visual analog scores; tear osmolarity; TBUT; corneal staining Secondary outcome(s): lid wiper epitheliopathy; meibum quality; tear film lipid layer thickness; tear meniscus height; Schirmer's test; meibomian gland expressibility

NCT02014922 *(Continued)*

	Adverse events: none reported
Starting date	December 2013
Contact information	Study sponsor: University of Waterloo; Advanced Vision Research Investigator: not reported
Notes	Status: completed November 2014

NCT02280473

Trial name or title	"A Safety and Efficacy Study of a New Eye Drop Formulation in Patients With Dry Eye Disease"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 188 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Current use of an artificial tear product • Visual acuity of at least 20/32 (while wearing glasses, if necessary)." Exclusion criteria: • "Use of contact lenses in the last 3 months, or anticipated use of contact lenses during the study • Cataract surgery, laser-assisted in situ keratomileusis [LASIK], or photorefractive keratectomy, within the last 6 months • Current eye infection or inflammation"
Interventions	Intervention #1: carboxymethylcellulose sodium based eye drop, 1 to 2 drops in each eye as needed at least 2 times daily Intervention #2: carboxymethylcellulose sodium 1.0% (REFRESH LIQUIGEL®), 1 to 2 drops in each eye as needed at least 2 times daily Length of follow-up: 30 days
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): TBUT; corneal staining; conjunctival staining; Schirmer's test Adverse events: none reported
Starting date	October 2014
Contact information	Study sponsor: Allergan Investigator: not reported
Notes	Status: completed March 2015

NCT02369861

Trial name or title	"Study of ACCS Eye Drops in Treating Dry Eye"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 30 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Subjects ages 18 years and older. • Subjects with symptoms and signs of Dry Eye for > four months supported by previous clinical diagnosis or self-reported history. • Visual acuity corrected 20/40 or better in each eye.If wearing contact lenses, subjects must be willing to refrain from wearing the contact lenses during the study (including washout period). • Score of 25-75 on the Ocular Surface Disorder Index (OSDI) questionnaire. • Corneal staining of grade 2 or more anywhere on the cornea (scale 0-4)." Exclusion criteria: • "Pregnant or breast feeding. • Anterior segment disease other than Dry Eye which in the opinion of the investigator would confound the study. • Macular and neovascular eye diseasesHistory of corneal surgery or LASIK (laser in situ keratomileusis) surgery in either eye within the past year. • Use of cyclosporine, steroid eye drops, serum eye drops, or any other eye medication (except for artificial tears) or experimental drug within the past 30 days. • Subjects with glaucoma or in whom glaucoma is suspected. • Use of anticholinergic drugs, antihistamines, beta-blockers, or tricyclic anti-depressants within the past 30 days. • Asymmetric punctal plugs or punctal cauterization within the past three months. • History of Stevens-Johnson disease, ocular cicatricial pemphigoid, alkali burn of the eye, or graft-versus-host disease. • Immune compromise for any reason.Kidney or liver function studies >2x the upper limit of normal. • Symptomatic abnormalities od the lid. • History of cancer within the past 5 years"
Interventions	Intervention #1: ACCS 4 times daily Intervention #2: Refresh Lubricant Eye Drops 4 times daily Length of follow-up: 6 weeks
Outcomes	Primary outcome(s): corneal staining with fluorescein Secondary outcome(s): lissamine staining; endothelial cell count; intraocular pressure; tear volume; assessment of structure and function of the eye; OSDI score Adverse events: none reported
Starting date	March 2015
Contact information	Study sponsor: David L Steed, MD (Stemnion, Inc.); US Navy Bureau of Medicine

NCT02369861 *(Continued)*	
	Investigator: Kathy Kelley, OD (Price Vision Group)
Notes	Status: recruiting

NCT02420834	
Trial name or title	"Dry Eye Treatment With Artificial Tears"
Methods	Study design: 4-arm randomized, cross-over, controlled trial Number randomized: 50 (estimated)
Participants	Country: United Kingdom Age: not reported Gender: both Inclusion criteria: • "subjective symptoms indicative of dry eye" Exclusion criteria: • "Diabetes • Sjögren's Syndrome • recent ocular infection • hay fever • used any eye drops or ocular medications, • were currently on medications known to affect the eyes • wore contact lenses • were pregnant."
Interventions	Intervention #1: preservative-free hypromellose eye drops BP 0.15%, applied as required Intervention #2: preservative-free hypromellose eye drops BP 0.4%, applied as required Intervention #3: preservative-free 0.25% carboxymethylcellulose, electrolyte balanced (Ther-atears), applied as required Intervention #4: preservative-free phospholipid liposomal spray (Tears Again), applied as required Length of follow-up: 4 months
Outcomes	Primary outcome(s): symptoms Secondary outcome(s): noninvasive break-up time; tear meniscus height; lid parallel conjunctival folds; ocular surface staining; phenol red test Adverse events: none reported
Starting date	April 2015
Contact information	Study sponsor: Aston University Investigator: James S Wolffsohn, BSc PhD (Aston University)
Notes	Status: ongoing, not recruiting

NCT02446015

Trial name or title	"Clinical Evaluation Following Use of SYSTANE® ULTRA in the Management of Dry Eye"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 110 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Willing and able to attend all study visits. • Use of BAK-free artificial tear drops on an as needed basis, at least once a week, within 3 months prior to Screening Visit (maximum use of 4 drops a day). • At least one '8 hour waking period' per week during the run-in phase without using the provided artificial tear. • Use provided artificial tear at least once a week during run-in phase. • Willing to take study treatment as directed for the entire study and able to complete the study diaries as required. • Other protocol-specified inclusion criteria may apply." Exclusion criteria: • "Use of artificial tears, as specified in the protocol. • Use of topical ocular medications, as specified in the protocol. • Women of childbearing potential who are pregnant, breast feeding, plan to become pregnant during the study, or not using adequate birth control methods to prevent pregnancy throughout the study. • Any hypersensitivity to the use of the study product formulations or an allergy to any ingredient(s) contained within product formulations. • Ocular abnormalities, infection, or active inflammation (not associated with dry eye) as specified in the protocol. • Ocular or intraocular surgery or serious ocular trauma in either eye within the past 6 months prior to Screening Visit. • Any medical condition (systemic or ophthalmic) that may preclude the safe administration of test article or safe participation in the study. • Contact lens use within 2 weeks prior to Screening Visit, and unwilling to avoid contact lens use during the course of the study. • Other protocol-specified exclusion criteria may apply."
Interventions	Intervention #1: Systane® Ultra lubricant eye drops,1 drop in each eye, 4 times per day Intervention #2: Systane® Ultra lubricant eye drops, 1 drop in each eye, as needed Length of follow-up: 28 days
Outcomes	Primary outcome(s): TOSS score Secondary outcome(s): IDEEL SB score; IDEEL TS scores Adverse events: none reported
Starting date	June 2015

NCT02446015 *(Continued)*

Contact information	Study sponsor: Alcon Research Investigator: not reported
Notes	Status: recruiting

NCT02455050

Trial name or title	"A Study to Compare a New Eye Drop Formulation With Systane® Gel Drops and Genteal® Lubricant Gel Drops for Moderate to Severe Dry Eye Relief"
Methods	Study design: 4-arm randomized, cross-over, controlled trial Number randomized: 84 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Current use of an artificial tear product • Visual Acuity of at least 20/40 (while wearing glasses, if necessary)." Exclusion criteria: • "Use of contact lenses in the last 3 months, or anticipated use of contact lenses during the study • Cataract surgery, laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy within 6 months • Use of RESTASIS® Cyclosporine Ophthalmic Emulsion or any topical cyclosporine within 3 months • Diagnosis of glaucoma."
Interventions	Intervention #1: 1 to 2 drops of new eye drop formulation (carboxymethylcellulose sodium-based eye drops) in each eye as needed at least 2 times daily for 2 weeks, followed by 1 to 2 drops of Systane® Gel Drops in each eye as needed at least 2 times daily for 2 weeks Intervention #2: 1 to 2 drops of Systane® Gel Drops in each eye as needed at least 2 times daily for 2 weeks, followed by 1 to 2 drops of new eye drop formulation (carboxymethylcellulose sodium-based eye drops) in each eye as needed at least 2 times daily for 2 weeks Intervention #3: 1 to 2 drops of Genteal® Lubricant Gel Drops in each eye as needed at least 2 times daily for 2 weeks, followed 1 to 2 drops of new eye drop formulation (carboxymethylcellulose sodium-based eye drops) in each eye as needed at least 2 times daily for 2 weeks Intervention #4: 1 to 2 drops of new eye drop formulation (carboxymethylcellulose sodium-based eye drops) in each eye as needed at least 2 times daily for 2 weeks, followed by 1 to 2 drops of Genteal® Lubricant Gel Drops in each eye as needed at least 2 times daily for 2 weeks Length of follow-up: 42 days
Outcomes	Primary outcome(s): tolerability Survey score Secondary outcome(s): OSDI score; Acceptability Survey score; SESoD score; comfort, blur, and relief of symptoms; distance visual acuity; TBUT; Eye Drop Experience Survey score Adverse events: none reported

NCT02455050 *(Continued)*

Starting date	December 2014
Contact information	Study sponsor: Allergan Investigator: not reported
Notes	Status: completed August 2015

NCT02470429

Trial name or title	"Evaluation of Clinical Outcomes After the Use of SYSTANE® HYDRATION"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 100 (estimated)
Participants	Country: United States Age: not reported Gender: both Inclusion criteria: • "Willing and able to attend all study visits; • Use of non-BAK (Benzalkonium Chloride) artificial tears at least once a day, for at least 3 months prior to Screening Visit; • Diagnosis of Dry Eye (by a health care professional) for at least 3 months prior to Screening Visit; • Other protocol-defined inclusion criteria may apply." Exclusion criteria: • "Women of childbearing potential who are pregnant or breast feeding; • Any hypersensitivity to the use of the study product formulations or an allergy to any ingredient(s) contained within product formulations; • Ocular abnormalities in either eye that could adversely affect the safety or efficacy outcome; • Active ocular infection (bacterial, viral, or fungal) or active inflammation not associated with dry eye; • Use of chronic systemic medications: (prescription, over the counter, vitamins/supplements) on a stable dose for less than 30 days prior to Screening Visit, or any anticipated change in dosing regimen during the course of the study; • History of ocular or intraocular surgery or serious ocular trauma in either eye within the past 6 months prior to Screening Visit; • Any medical condition (systemic or ophthalmic) that may, in the opinion of the Investigator, preclude the safe administration of test article or safe participation in the study; • Use of any topical ocular over-the-counter or prescribed medications in either eye (with the exception of artificial tears/gels/ lubricants) 2 weeks prior to Screening Visit; • Contact lens use within 2 weeks prior to Screening Visit and unwilling to avoid contact lens use during the course of the study; • Unwilling to avoid use of additional artificial tears (other than study medication) throughout the study; • Other protocol-defined exclusion criteria may apply."
Interventions	Intervention #1: Systane Hydration lubricant eye drops, 1 drop 4 times per day in each eye Intervention #2: Hyabak 0.15% eye drops, 1 drop 4 times per day in each eye

NCT02470429 *(Continued)*

	Length of follow-up: 42 days
Outcomes	Primary outcome(s): TOSS score Secondary outcome(s): IDEEL Treatment Satisfaction scores; TBUT Adverse events: none reported
Starting date	July 2015
Contact information	Study sponsor: Alcon Research Investigator: not reported
Notes	Status: recruiting

NCT02507934

Trial name or title	"Tolerability, Safety and Efficacy of Lubricin (150 µg/ml) Eye Drops Versus Sodium Hyaluronate (HA) 0.18% Eye Drops in Patients With Moderate Dry Eye (DE)"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 40 (estimated)
Participants	Country: Italy Age: not reported Gender: both Inclusion criteria: To be checked at the screening visit (V1) within 7 days before study treatment and confirmed at baseline visit (V2): • "Patients 18 years of age or older. • Patients with moderate dry eye characterized by at least one eye with signs and symptoms of moderate dry eye (grade 2 or 3 of the 2007 DEWS report) • Patients diagnosed with dry eye from at least 3 months (current use or recommended use of artificial tears for the treatment of Dry Eye) • Average VAS score for typical symptoms of Dry Eye (foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ≥ 25 mm; • Corneal staining score with fluorescein > 3 using the Oxford corneal grading system in the worst performing eye; • Schirmer test without anaesthesia ≤ 10 mm/5 minutes in the worst performing eye; • Tear film break-up time (TBUT) ≤ 10 seconds in the worst performing eye • Best corrected distance visual acuity (BCDVA) score ≥ 0.1 decimal units in both eyes at the time of study enrollment. • Only patients who satisfy all Informed Consent requirements may be included in the study. The patient and/or his/her legal representative must read, sign and date the Informed Consent document before any study-related procedures are performed. The Informed Consent form signed by patients and/or legal representative must have been approved by the Ethics Committee for the current study." Exclusion criteria:

NCT02507934 *(Continued)*

- "Patients with a mild Dry Eye condition (severity level 1 according to the Report of the International Dry Eye Workshop -DEWS, 2007)
- Patients with a severe Dry Eye condition (severity level 4 according to the Report of the International Dry Eye Workshop -DEWS, 2007)
- Best corrected distance visual acuity (BCDVA) score of < 0.1 decimal units in either eye at the time of study enrolment
- Evidence of an active ocular infection in either eye
- History or presence of ocular surface disorders not related to dry eye in either eye
- Use of any ocular topical medication other than the study medications for the treatment of ocular diseases including artificial tears during the study period
- Use of topical cyclosporine, topical corticosteroids or any other topical medication for the treatment of dry eye in either eye within 30 days of study enrolment
- History of any ocular surgery (including laser or refractive surgical procedures) in either eye within the 90 days before study enrolment. Ocular surgery will not be allowed during the study treatment period and elective ocular surgery procedures should not be planned during the duration of the follow-up period
- Presence or history of any ocular or systemic disorder or condition that might significantly hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct of trail procedures (e.g. ocular trauma, progressive or degenerative corneal conditions, uveitis, systemic infection.)
- Known hypersensitivity to one of the components of the study or procedural medications
- Participation in another clinical study at the same time as the present study or within 90 days of screening/baseline visit
- History of drug, medication or alcohol abuse or addiction.
- Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:
  - are currently pregnant or,
  - have a positive result on the urine pregnancy test at the Screening/Baseline Visit or,
  - intend to become pregnant during the study treatment period or,
  - are breast-feeding or,
  - not willing to use highly effective birth control measures, such as: Hormonal contraceptives - oral, implanted, transdermal, or injected and/or mechanical barrier methods - spermicide in conjunction with a barrier such as a condom or diaphragm or an Intra Uterine Device during the entire course of and 30 days after the study treatment periods."

Interventions	Intervention #1: Lubricin 150 µg/ml eye drops solution Intervention #2: sodium hyaluronate 0.18% eye drops Length of follow-up: 2 weeks
Outcomes	Primary outcome(s): pretreatment adverse events; foreign body sensation; burning/stinging; itching; pain; sticky feeling; blurred vision; photophobia; treatment-emergent adverse events Secondary outcome(s): corneal fluorescein surface staining; TBUT; SANDE; Schirmer's test; BCVA Adverse events: yes
Starting date	June 2015
Contact information	Study sponsor: Dompé Farmaceutici S.p.A Investigator: Aessandro Lambiase, MD (Dipartimento "Organi di Senso" Università La Sapienza-Policlinico Umberto)
Notes	Status: completed August 2015

NCT02510235

Trial name or title	"Tolerability, Safety and Efficacy of Lubricin Eye Drops Versus Sodium Hyaluronate Eye Drops in Subjects With Moderate Dry Eye"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 56 (estimated)

Participants	Country: Italy
	
	Age: not reported
	
	Gender: both
	
	Inclusion criteria:
	
	"To be checked at the screening visit (V1) from day -14 to day -8 days before run-in period and confirmed at baseline visit (V2):
	
	• Subjects 18 years of age or older.
	• Subjects with moderate dry eye characterized by tear film osmolarity > 312 mOsm
	• Subjects with both VAS for frequency and severity of symptoms, SANDE items, at screening & baseline > 25 mm (SANDE overall score > 25 mm).
	• Subjects with moderate dry eye characterized by at least one eye with signs and symptoms of moderate dry eye (grade 2 or 3 of the 2007 DEWS report)
	• Subjects diagnosed with dry eye from at least 6 months (current use or recommended use of artificial tears/lubricants for the treatment of Dry Eye)
	• Best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units in both eyes at the time of study enrolment.
	• The Informed Consent by approved Ethics Committees should be signed by the subject before any study procedures."
	
	Exclusion criteria:
	
	• "Evidence of an active ocular infection in either eye
	• History or presence of ocular surface disorders not related to dry eye in either eye
	• History or evidence of eyelid abnormality in either eye
	• Use of topical cyclosporine, topical corticosteroids or any other topical medication for the treatment of dry eye in either eye within 30 days of study enrolment
	• History of any ocular surgery (including laser or refractive surgical procedures) in either eye within the 90 days before study enrolment. Ocular surgery will not be allowed during the study treatment period and elective ocular surgery procedures should not be planned during the duration of the follow-up period
	• Presence or history of any ocular or systemic disorder or condition that might significantly hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct of trail procedures (e.g. ocular trauma, progressive or degenerative corneal conditions, uveitis, systemic vasculitis, collagen vascular diseases, poorly controlled diabetes, autoimmune disease, systemic infection.)
	• Known hypersensitivity to one of the components of the study or procedural medications
	• Participation in another clinical study at the same time as the present study or within 90 days of baseline visit
	• History of drug, medication or alcohol abuse or addiction.
	• Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:
	  ○ are currently pregnant or,
	  ○ have a positive result on the urine pregnancy test at the Screening/Baseline Visit or,

NCT02510235 *(Continued)*

	○ intend to become pregnant during the study treatment period or, ○ are breast-feeding or, ○ not willing to use highly effective birth control measures, such as: Hormonal contraceptives - oral, implanted, transdermal, or injected and/or mechanical barrier methods - spermicide in conjunction with a barrier such as a condom or diaphragm or IUD during the entire course of and 30 days after the study treatment periods."
Interventions	Intervention #1: Lubricin 150 µg/ml eye drops solution Intervention #2: sodium hyaluronate 0.13% eye drops Length of follow-up: 28 days
Outcomes	Primary outcome(s): SANDE Secondary outcome(s): Ocular Total Tolerability Score; corneal fluorescein surface staining; tear osmolarity; TBUT; BCVA; treatment-emergent adverse events Adverse events: yes
Starting date	March 2015
Contact information	Study sponsor: Dompé Farmaceutici S.p.A Investigator: Caterina Gagliano, MD (Azienda Ospedaliero Universitaria "Policlinico Vittorio Emanuele" Presidio Ospedaliero, Gaspare Rodolico Clinica Oculistica)
Notes	Status: completed May 2015

NCT02553772

Trial name or title	"A Safety and Efficacy Study of a New Eye Drop Formulation in Patients With Dry Eye Disease"
Methods	Study design: randomized, parallel-group, controlled trial Number randomized: 242 (estimated)
Participants	Country: Australia; United States Age: not reported Gender: both Inclusion criteria: • "Used artificial tears for dry eye • Visual acuity of at least 20/32 (while wearing glasses, if necessary)." Exclusion criteria: • "Use of contact lenses in the last 3 months, or anticipated use of contact lenses during the study • Herpes keratitis in the last 6 months • Cataract surgery, laser-assisted in situ keratomileusis [LASIK], or photorefractive keratectomy, within the last 6 months"
Interventions	Intervention #1: carboxymethylcellulose-based eye drop administered as 1 to 2 drops in each eye, as needed, at least twice daily

NCT02553772 *(Continued)*

	Intervention #2: carboxymethylcellulose sodium 0.5% (REFRESH OPTIVE® ADVANCED) administered as 1 to 2 drops in each eye, as needed, at least twice daily Length of follow-up: 90 days
Outcomes	Primary outcome(s): OSDI score Secondary outcome(s): TBUT; corneal staining; conjunctival staining; Schirmer's test Adverse events: none reported
Starting date	January 2016
Contact information	Study sponsor: Allergan Investigator: not reported
Notes	Status: recruiting

NCT02585453

Trial name or title	"Influence of Lachrymal Substitute Gels on Tear Film Thickness in Patients With Moderate to Severe Dry Eye Syndrome"
Methods	Study design: 3-arm randomized, parallel-group, controlled trial Number randomized: 60 (estimated)
Participants	Country: Austria Age: not reported Gender: both Inclusion criteria: • "Men and women aged over 18 years • Signed and dated written informed consent • History of dry eye syndrome for at least 3 months • Tear Break Up Time (BUT) ≤ 10 seconds or Schirmer I test ≤ 5 mm and ≥ 2mm • OSDI ≥ 22 • Normal ophthalmic findings except dry eye syndrome, ametropia < 6 Dpt. • No administration of topical lubricants 12-24 hours before the screening examination" Exclusion criteria: • "Presence of an ocular pathology judged by the investigator as incompatible with the study. • Any other clinical relevant ocular abnormality except DES. • History of allergy, known hypersensitivity to one of the components: the study medications or Fluorescein. • History of known clinically relevant allergy. • Medical or surgical history judged by the investigator to be incompatible with the study participation (hepatic or renal insufficiency; all chronic severe organic disease: metabolic, endocrine, neoplastic, haematological disease; severe psychiatric illness, etc.). • History of a recent acute illness with a recovery period within the 2 weeks before the inclusion visit (Day 0). • Pregnancy, lactation.

NCT02585453 *(Continued)*

	• Pre-menopausal woman who is not using a reliable birth control method (oral contraceptives or coil) or is not surgically sterilised. • Participation in any high-speed or water-sports during the study without ocular protection (goggles or glasses). • Subject unable to understand the study instructions or unlikely to comply with the study schedule and treatment. • Participation in another clinical study in the 4 weeks before the start of the present study or at the same time as the present study. • Subject is a ward of court."
Interventions	Intervention #1: Thealoz Duo Gel Intervention #2: Hylo-Gel Intervention #3: Systane Gel Drops Length of follow-up: 1 month
Outcomes	Primary outcome(s): tear film thickness Secondary outcome(s): TBUT; Schirmer's test; subjective evaluation of ocular comfort Adverse events: none reported
Starting date	April 2015
Contact information	Study sponsor: Medical University of Vienna Investigator: Gerhard Garhofer (Medical University of Vienna)
Notes	Status: completed September 2015

NCT02585648

Trial name or title	"Added Benefits of Lachrymal Substitute Gel During the Night in Patients With Moderate to Severe Dry Eye Syndrome"
Methods	Study design: randomized, cross-over, controlled trial Number randomized: 40 (estimated)
Participants	Country: Austria Age: not reported Gender: both Inclusion criteria: • "Men and women aged over 18 years • Signed and dated written informed consent. • History of dry eye syndrome for at least 3 months • Tear Break Up Time (BUT) ≤ 10 seconds or Schirmer I test ≤ 5 mm and ≥ 2mm • OSDI ≥ 22 • Normal ophthalmic findings except dry eye syndrome • No administration of topical lubricants 24 hours before the screening examination" Exclusion criteria:

NCT02585648 *(Continued)*

	• "Presence of an ocular pathology judged by the investigator as incompatible with the study. • Any other clinical relevant ocular abnormality except DES. • History of allergy, known hypersensitivity to one of the components: the administered medical device product, fluorescein or lissamine green • History of known clinically relevant allergy • Medical or surgical history judged by the investigator to be incompatible with the study participation (hepatic or renal insufficiency; all chronic severe organic disease: metabolic, endocrine, neoplastic, hematological disease; severe psychiatric illness, etc.). • History of a recent acute illness with a recovery period within the 2 weeks before the inclusion visit (Day 0). • Pregnancy, lactation. • Pre-menopausal woman who is not using a reliable birth control method (oral contraceptives or coil) or is not surgically sterilized. • Participation in any high-speed or water-sports during the study without ocular protection (goggles or glasses). • Subject unable to understand the study instructions or unlikely to comply with the study schedule and treatment. • Participation in another clinical study in the 4 weeks before the start of the present study or at the same time as the present study."
Interventions	Intervention #1: Thealoz Duo gel at night (1 drop before going to bed) + Thealoz Duo eye drops during the day (4 to 6 drops per day), and then cross over to Thealoz Duo eye drops during the day (4 to 6 drops per day) Intervention #2: Thealoz Duo eye drops during the day (4 to 6 drops per day), and then cross over to Thealoz Duo gel at night (1 drop before going to bed) + Thealoz Duo eye drops during the day (4 to 6 drops per day) Length of follow-up: 4 weeks
Outcomes	Primary outcome(s): patient satisfaction Secondary outcome(s): quality of life; number of drops of Thealoz Duo instilled during the day; TBUT; conjunctival staining; Schirmer's test; OSDI score Adverse events: none reported
Starting date	November 2015
Contact information	Study sponsor: Medical University of Vienna Investigator: Gerhard Garhofer (Medical University of Vienna)
Notes	Status: not yet recruiting

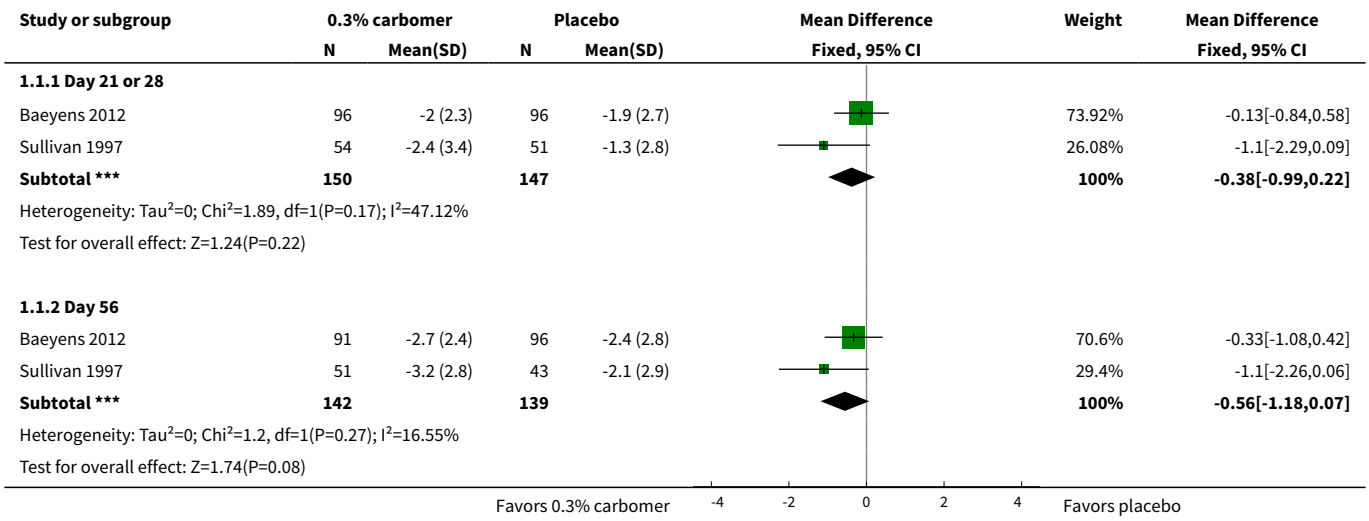
BCVA: best-corrected visual acuity
IDEEL: impact of dry eye on everyday life
OSDI: ocular surface disease index
SANDE: symptom assessment in dry eye
SD: standard deviation
secs: seconds
SESoD: subjective evaluation of symptom of dryness
TBUT: tear break-up time
TOSS: total ocular surface staining
VAS: visual analog scale

DATA AND ANALYSES

Comparison 1. 0.3% carbomer versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in symptom scores	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Day 21 or 28	2	297	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.99, 0.22]
1.2 Day 56	2	281	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.18, 0.07]

Analysis 1.1. Comparison 1 0.3% carbomer versus placebo, Outcome 1 Mean change in symptom scores.

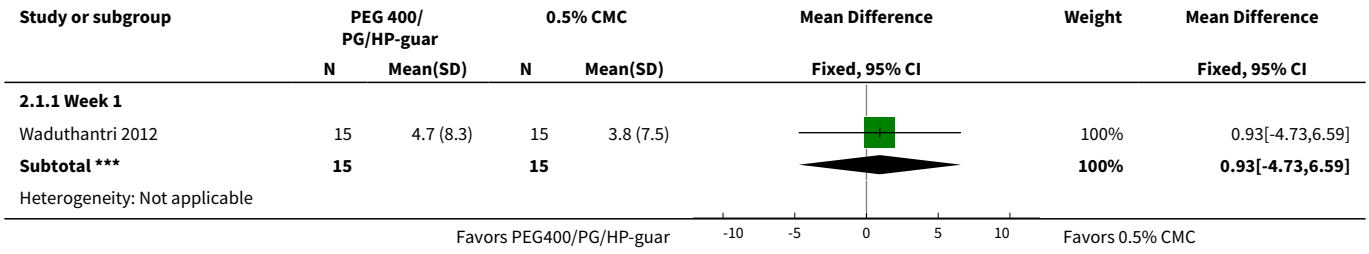


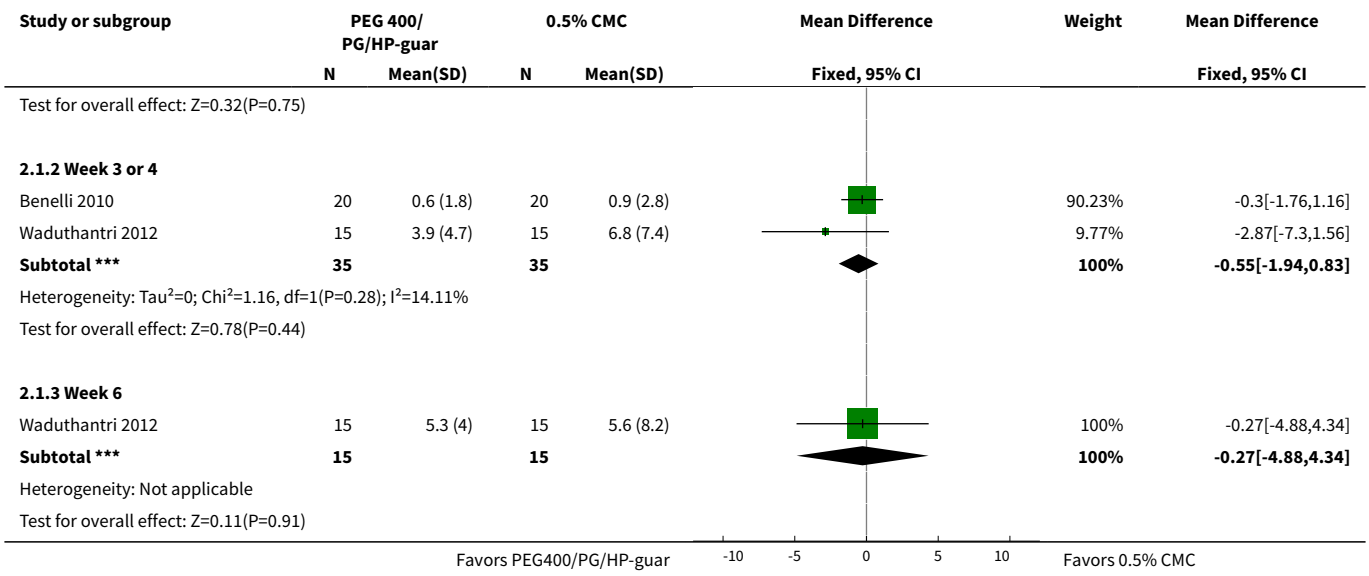
Comparison 2. Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in Schirmer's test	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Week 1	1	30	Mean Difference (IV, Fixed, 95% CI)	0.93 [-4.73, 6.59]
1.2 Week 3 or 4	2	70	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-1.94, 0.83]
1.3 Week 6	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-4.88, 4.34]
2 Mean change in TBUT	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Week 1	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

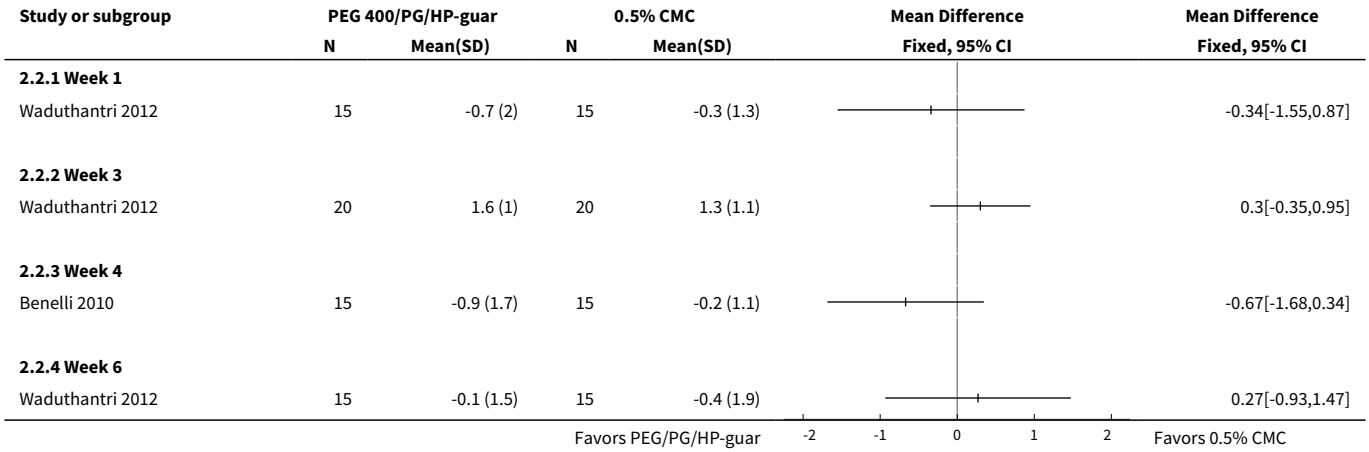
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Week 3	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Week 4	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Week 6	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mean corneal fluorescein staining score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Week 1	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.01, 0.20]
3.2 Week 2	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-1.49, -0.24]
3.3 Week 4	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-1.05, 0.14]
3.4 Week 6	2	242	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.59, -0.31]
4 Mean conjunctival lissamine green staining score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Week 1	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.44, 0.16]
4.2 Week 2	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.41, 0.31]
4.3 Week 4	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.58, 0.16]
4.4 Week 6	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.20, -0.40]
5 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Number of participants who experienced at least one adverse event	2	252	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.34, 3.80]
5.2 Number of participants who discontinued the trial due to adverse event	3	339	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.91]

Analysis 2.1. Comparison 2 Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium, Outcome 1 Mean change in Schirmer's test.

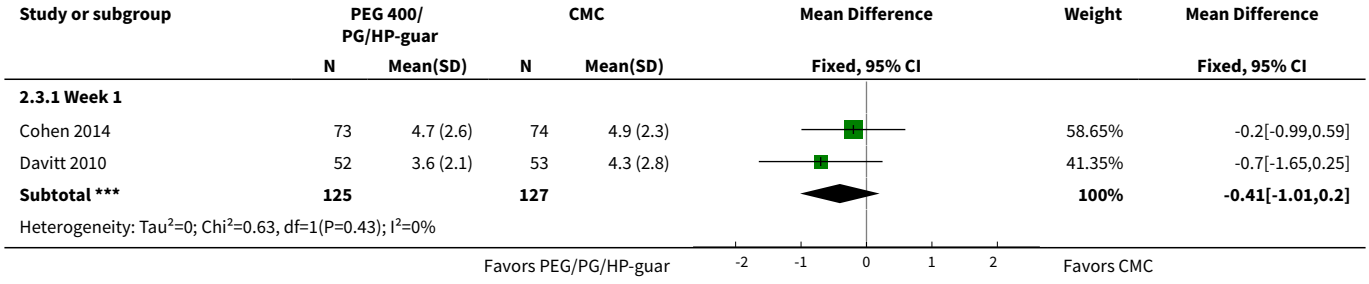


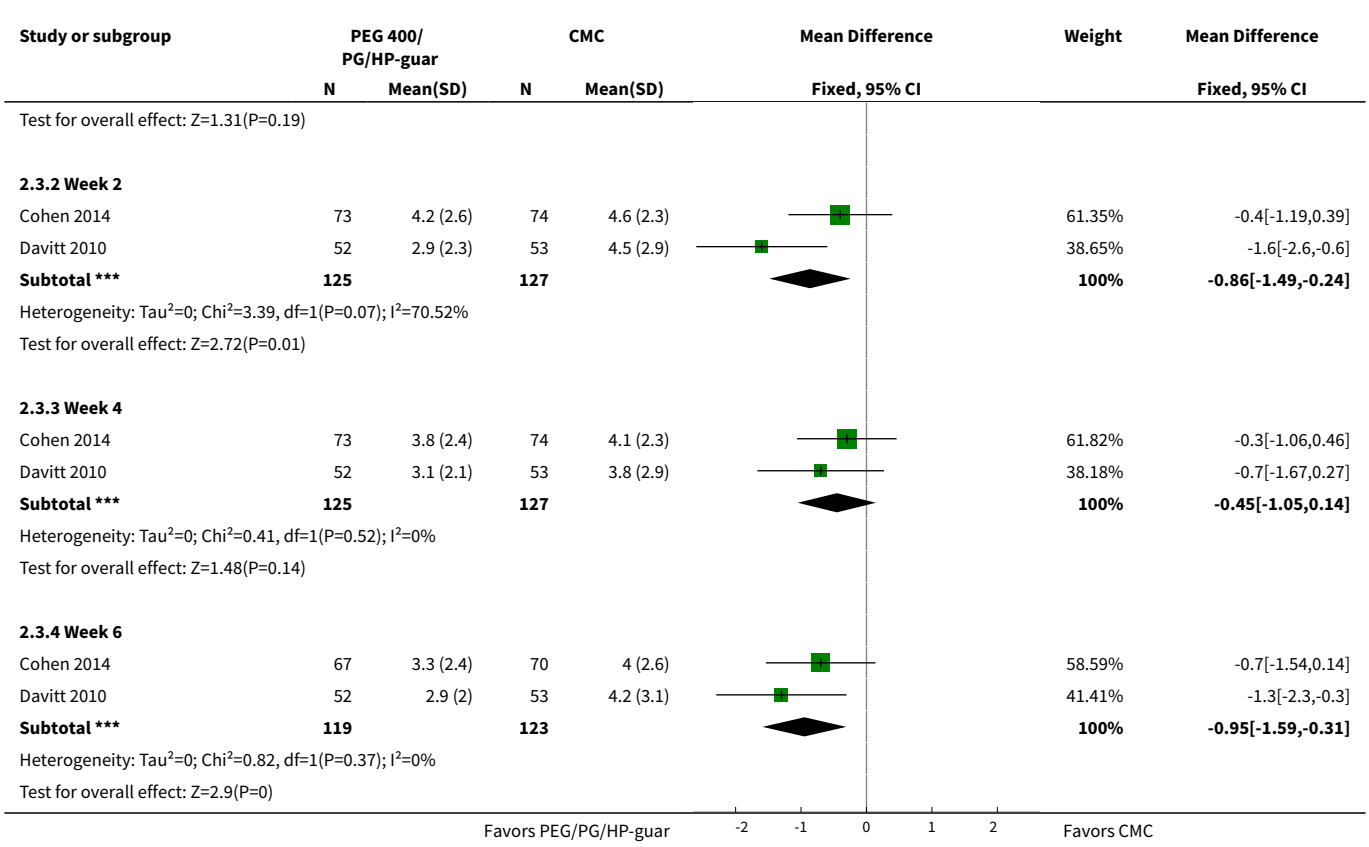


Analysis 2.2. Comparison 2 Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium, Outcome 2 Mean change in TBUT.

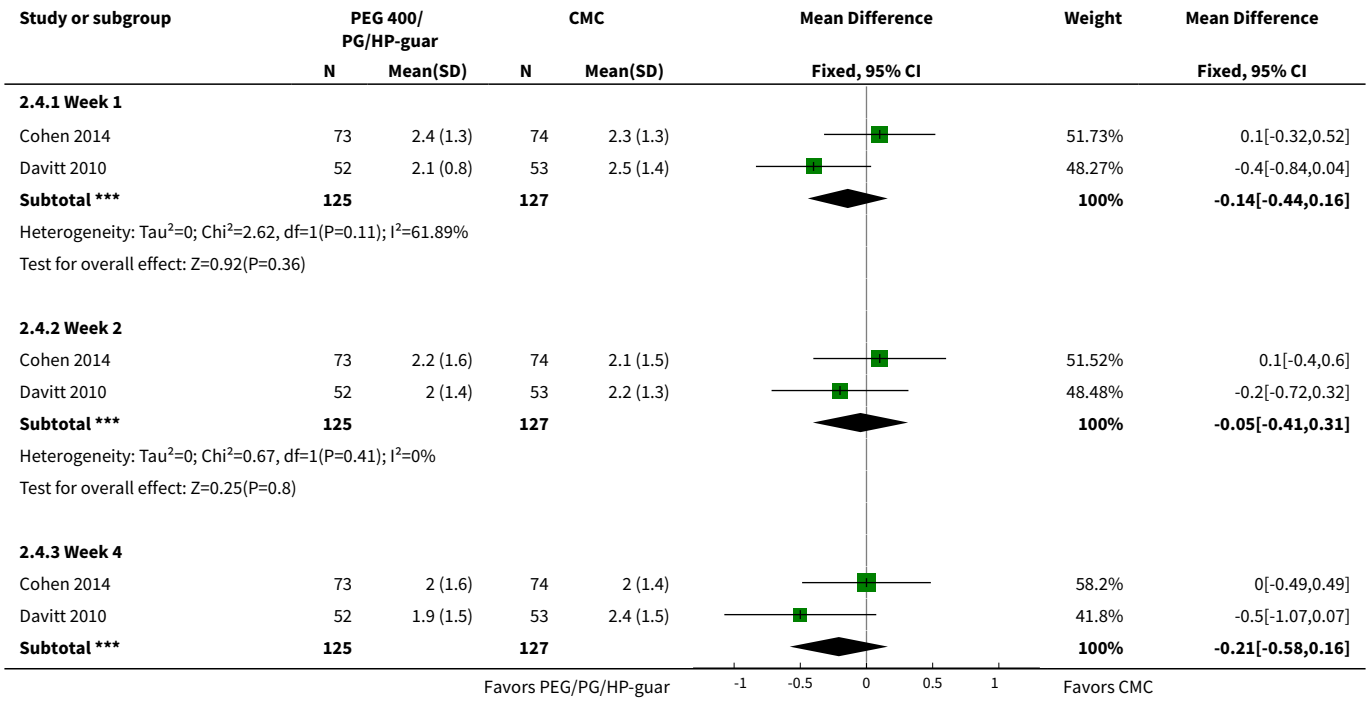


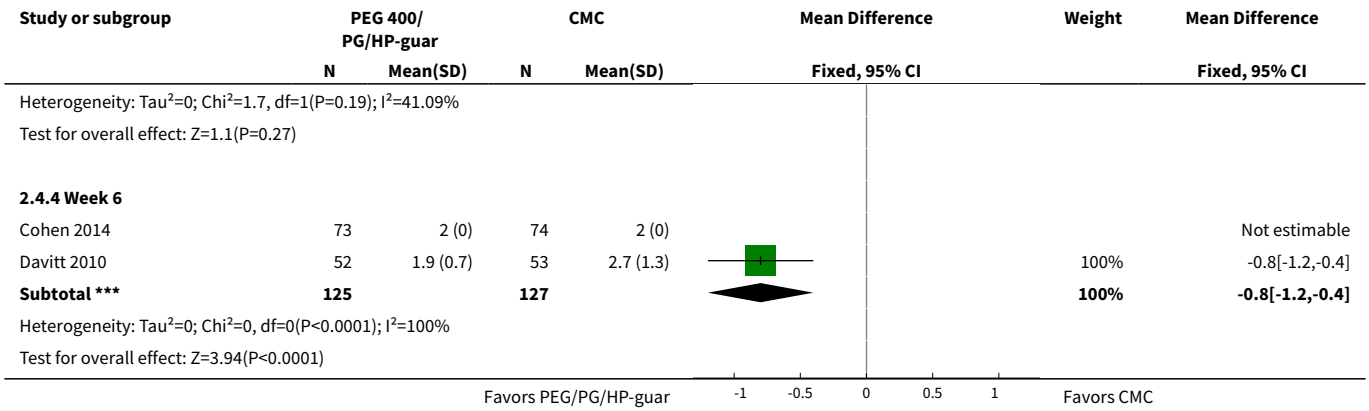
Analysis 2.3. Comparison 2 Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium, Outcome 3 Mean corneal fluorescein staining score.



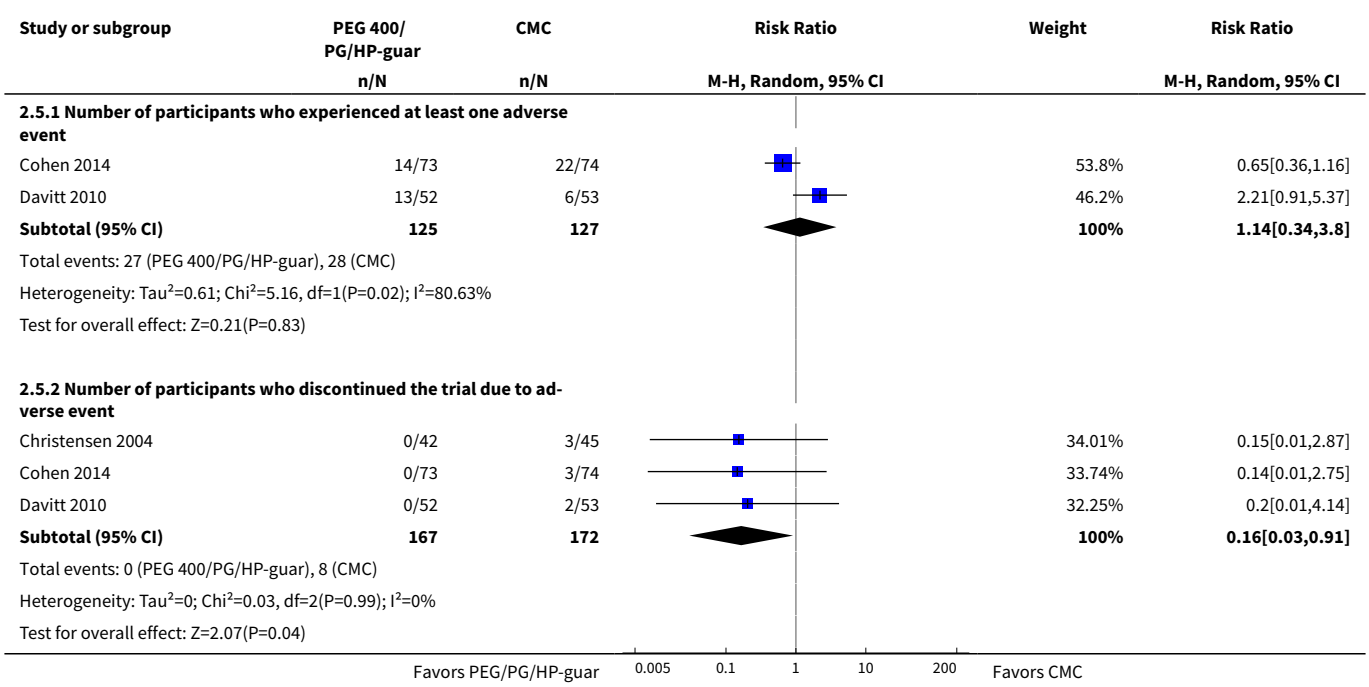


Analysis 2.4. Comparison 2 Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium, Outcome 4 Mean conjunctival lissamine green staining score.





Analysis 2.5. Comparison 2 Polyethylene glycol (PEG) 400 plus propylene glycol (PG) plus hydroxypropyl (HP) guar-based ophthalmic gel versus carboxymethylcellulose (CMC) sodium, Outcome 5 Adverse events.



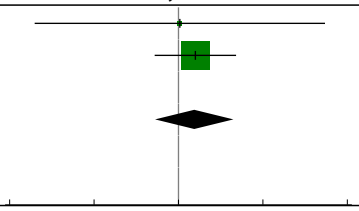
Comparison 3. 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change from baseline in symptom scores at Month 1	2	131	Mean Difference (IV, Fixed, 95% CI)	0.93 [-1.39, 3.25]
2 Mean change in TBUT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Month 1	2	131	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.40, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Month 2	1	65	Mean Difference (IV, Fixed, 95% CI)	0.7 [-0.29, 1.69]
3 Mean change in corneal staining score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Month 1	2	131	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.53, 0.24]
3.2 Month 2	1	65	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.58, 0.78]
3.3 Month 3	1	62	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.29, 0.69]
4 Mean change in total ocular staining score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Month 1	1	66	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.05, 1.05]
4.2 Month 3	2	110	Mean Difference (IV, Fixed, 95% CI)	0.46 [-0.48, 1.40]

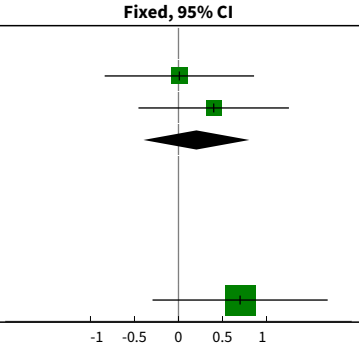
Analysis 3.1. Comparison 3 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate, Outcome 1 Mean change from baseline in symptom scores at Month 1.

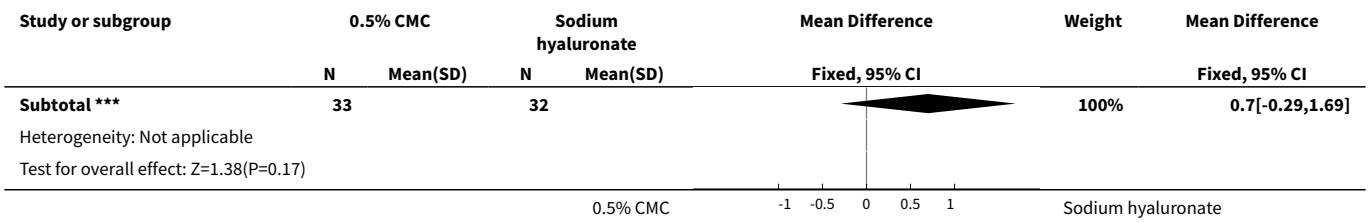
Study or subgroup	0.5% CMC		Sodium hyaluronate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Baudouin 2012	37	-13.6 (19.1)	29	-13.7 (16.5)		7.29%	0.08[-8.52,8.68]
Lee 2011	33	-4.4 (4.3)	32	-5.4 (5.5)		92.71%	1[-1.41,3.41]
Total ***	**70**		**61**			**100%**	**0.93[-1.39,3.25]**
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%							
Test for overall effect: Z=0.79(P=0.43)							



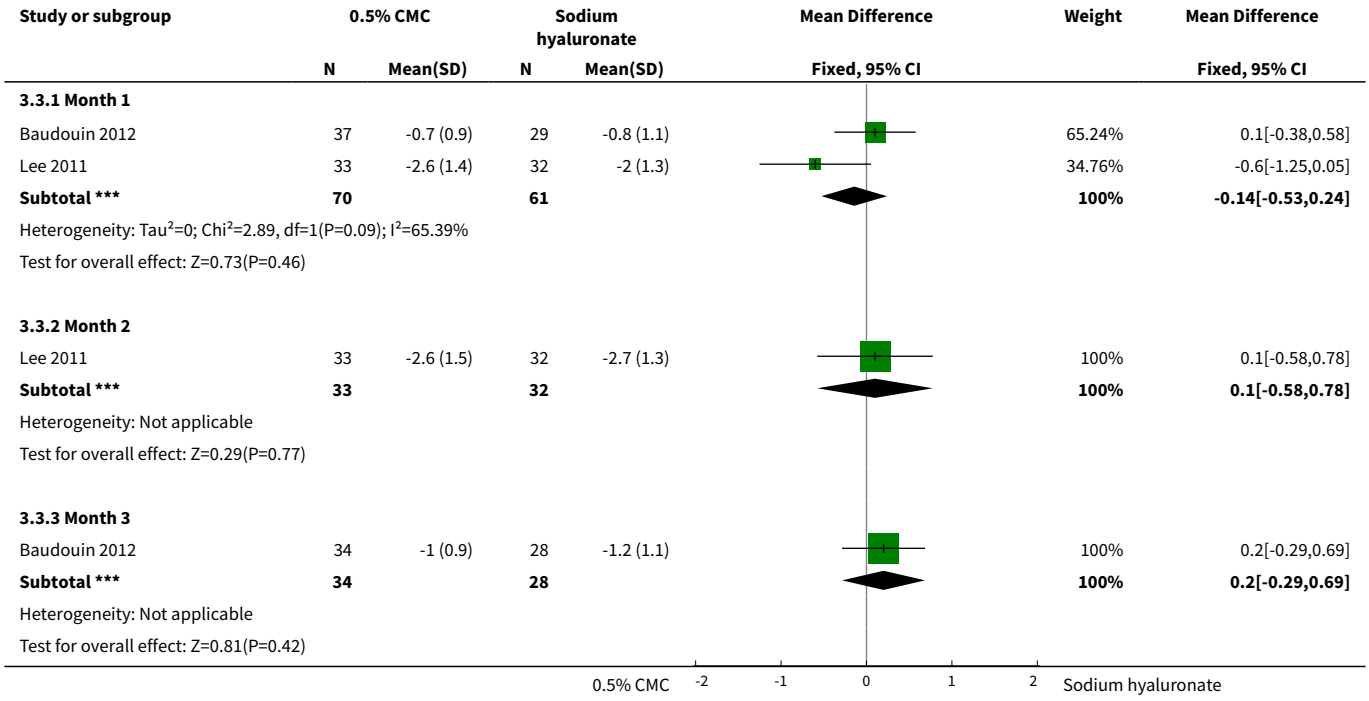
Analysis 3.2. Comparison 3 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate, Outcome 2 Mean change in TBUT.

Study or subgroup	0.5% CMC		Sodium hyaluronate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
3.2.1 Month 1							
Baudouin 2012	37	0.3 (1.7)	29	0.3 (1.8)		50.36%	0.01[-0.84,0.86]
Lee 2011	33	1.5 (1.7)	32	1.1 (1.8)		49.64%	0.4[-0.45,1.25]
Subtotal ***	**70**		**61**			**100%**	**0.2[-0.4,0.81]**
Heterogeneity: Tau²=0; Chi²=0.4, df=1(P=0.53); I²=0%							
Test for overall effect: Z=0.66(P=0.51)							
3.2.2 Month 2							
Lee 2011	33	2.5 (2.1)	32	1.8 (2)		100%	0.7[-0.29,1.69]

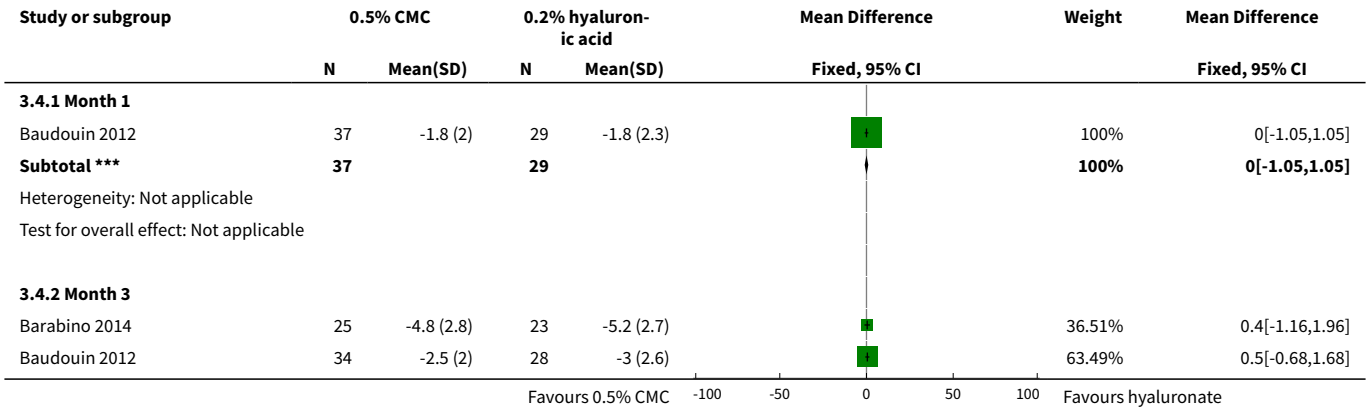


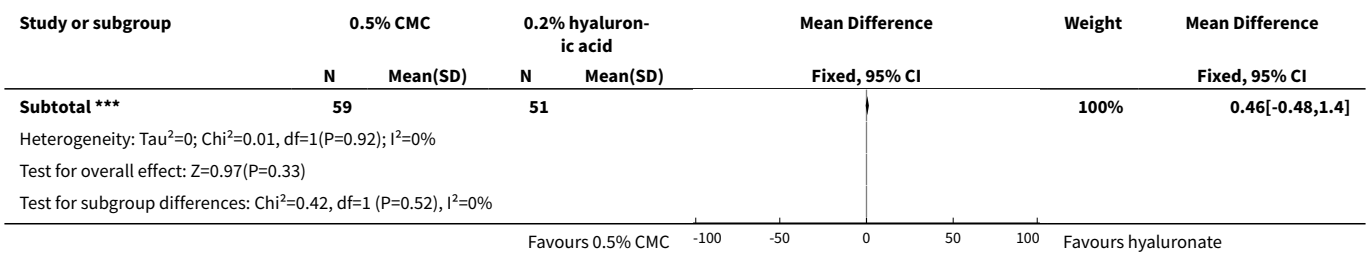


Analysis 3.3. Comparison 3 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate, Outcome 3 Mean change in corneal staining score.



Analysis 3.4. Comparison 3 0.5% carboxymethylcellulose(CMC) versus sodium hyaluronate, Outcome 4 Mean change in total ocular staining score.





ADDITIONAL TABLES

Table 1. US Food and Drug Administration component descriptions for over the counter artificial tear drops

Demulcents	Emollients
Cellulose derivatives 1. Carboxymethylcellulose sodium, 0.2% to 2.5% 2. Hydroxyethyl cellulose, 0.2% to 2.5% 3. Hydroxypropyl methylcellulose, 0.2% to 2.5% 4. Methylcellulose, 0.2% to 2.5%	*Lanolin preparations* 1. Anhydrous lanolin, 1% to 10% in combination with one or more oleaginous emollient agents 2. Lanolin, 1% to 10% in combination with one or more oleaginous emollient agents
Dextran 70 0.1% when used with another polymeric demulcent agent	*Oleaginous ingredients* 1. Light mineral oil, up to 50% in combination with one or more emollient agents 2. Mineral oil, up to 50% in combination with one or more emollient agents 3. Paraffin, up to 5% in combination with one or more emollient agents 4. Petrolatum, up to 100% 5. White ointment, up to 100% 6. White petrolatum, up to 100% 7. White wax, up to 5% in combination with one or more emollient agents 8. Yellow wax, up to 5% in combination with one or more emollient agents
Gelatin 0.01%	
Liquid polyols 1. Glycerin, 0.2% to 1% 2. Polyethylene glycol 300, 0.2% to 1% 3. Polyethylene glycol 400, 0.2% to 1% 4. Polysorbate 80, 0.2% to 1% 5. Propylene glycol, 0.2% to 1%	
Polyvinyl alcohol 0.1% to 4%	
Povidone 0.1% to 2%	

FDA 2015

Table 2. Summary of study design, study participants, interventions, and follow-up periods

Study ID Study design	Condition(s) included	Number of randomized participants	Interventions studied			Follow-up period(s)
Aguilar 2014 Randomized, parallel-group, controlled trial	Lipid-deficient dry eye and meibomian gland dysfunction	51	0.6% PG/HP-guar (Systane® Balance)		Saline	4 weeks
Baeyens 2012 Randomized, parallel-group, controlled trial	Moderate dry eye	304	0.3% carbomer	0.18% sodium hyaluronate	Placebo (saline)	4, 8, and 12 weeks
Barabino 2014 Randomized, parallel-group, controlled trial	Moderate dry eye	48	0.5% CMC/0.9% glycerin (Optive monodose)		0.2% hyaluronic acid/0.2% tamarind seed polysaccharide (Xiloial monodose)	2, 4, 6, 8, and 12 weeks
Baudouin 2012 Randomized, parallel-group, controlled trial	Keratoconjunctivitis sicca	82	0.5% CMC (Optive multi-dose)		0.18% sodium hyaluronate (Vismed® Multi)	35 days, and 3 months
Benelli 2010 Randomized, parallel-group, controlled trial	Dry eye	60	0.5% CMC (Cellufresh®)	2.5% PEG 400 (Blink® Intensive Tears)	0.18% HP-guar /PEG 400/PG (Systane®)	4 weeks
Boisjoly 2003 Randomized, crossover, controlled trial	Moderate to severe dry eye	22	1% CMC (Refresh Liquigel™)		0.3% HPMC/0.22% carbomer (GenTeal® Gel)	4 weeks each phase

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Brignole 2005 Randomized, parallel-group, controlled trial	Moderate dry eye	22	1% CMC (Celluvisc)	0.18% sodium hyaluronate (Vismed)	8 weeks
Brodwall 1997 Randomized, parallel-group, controlled trial	Dry eye	85	0.2% PAA (Visco tears®)	1.4% PVA	4 weeks
Bron 1998a Randomized, parallel-group, controlled trial	Aqueous-deficient dry eye	179	0.2% carbomer 940 (Lacrinorm/GelTears, Laboratoire Chauvin)	0.2% carbomer 940 (Viscotears/Vidisic/Lacrigel)	4 weeks
Bron 1998b Randomized, parallel-group, controlled trial	Moderate dry eye	90	0.2% PAA/carbomer (Viscotears®)	1.4% PVA (Liquifilm®)	3, and 6 weeks
Bruix 2006 Randomized, parallel-group, controlled trial	Mild or moderate dry eye	19	0.5% CMC (Cellufresh®)	Placebo (saline)	3, 6, and 12 weeks
Cohen 2014 Randomized, parallel-group, controlled trial	Dry eye	147	1% CMC (Refresh LiquiGel®)	0.4% PEG400/0.3% PG/HP-guar (Systane®Gel)	1, 2, 4, and 6 weeks
Comez 2013 Randomized, parallel-group, controlled trial	Moderate to severe dry eye	43	0.4% PEG 400/0.3% PG (Systan®) (right eye) 15% sodium hyaluronate (Eyestil®) (left eye)	0.3% HPMC (Tears Naturale®) (right eye) 0.5% CMC (Refresh® Tears)	2, 4, and 12 weeks
Christensen 2004	Dry eye	87	0.4% PEG 400/0.3% PG/HP-guar (Systane™ Lubricant Eye Drops)	0.5% CMC (Refresh Tears® Lubricant Eye Drops)	1, 2, 4, and 6 weeks

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Randomized, parallel-group, controlled trial						
Christensen 2009 Randomized, parallel-group, controlled trial	Dry eye	105	0.4% PEG 400/0.3% PG (Systane® Ultra Lubricant Eye Drops)		0.5% CMC (Optive ™)	2, 4, and 6 weeks
Davitt 2010 Randomized, parallel-group, controlled trial	Dry eye	105	PEG 400/PG/HP-guar		0.5% CMC (Optive™ Lubricant Eye Drops)	1, 2, 4, and 6 weeks
Donshik 1998 Trial 1 Randomized, parallel-group, controlled trial	Moderate to severe Keratoconjunctivitis sicca	27	0.3% HPMC (BION Tears)		0.3% HPMC	1, 4, and 8 weeks
Donshik 1998 Trial 2 Randomized, parallel-group, controlled trial	Moderate to severe Keratoconjunctivitis sicca	41	0.3% HPMC (BION Tears)	0.2% PEG 400 (AquaSite)	0.5% CMC (Cellufresh)	3, 6, 9, and 12 weeks
Donshik 1998 Trial 3 Randomized, parallel-group, controlled trial	Moderate to severe Keratoconjunctivitis sicca	124	0.3% HPMC (BION Tears)		0.5% CMC (Refresh Plus)	3, 6, 9, and 12 weeks
Dumbleton 2009 Randomized, parallel-group, controlled trial	Moderate to severe dry eye	110	0.25% PEG 400 (Blink® gel tears)		1% CMC (Refresh Liquigel®)	7, 15 and 30 days
Foley-Nolan 1995	Dry eye	91	0.2% PAA (Viscotears)		1.4% PVA	3 and 6 weeks

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Randomized, parallel-group, controlled trial					
Garcia-Lazaro 2011 Randomized, crossover, controlled trial	Dry eye	20	2.5% PEG 400 (Blink Intensive Tears)	0.3% HPMC (Artific Tears)	1 month each phase
Grene 1992 Randomized, parallel-group, controlled trial	Keratoconjunctivitis sicca	56	1.0% CMC (Celluvisc Lubricant Ophthalmic solution)	0.3% HPMC (Tears Naturale 2 Lubricant Eye Drops)	1, 4, and 8 weeks
Huth 2008 Randomized, crossover, controlled trial	Dry eye	NR	0.25% PEG 400 (Blink Tears® Lubricant Eye Drops)	0.4% PEG 400/0.3% PG glycol (Systane® Lubricant Eye Drops)	1, and 14 days
Iester 2000 Randomized, parallel-group, controlled trial	Moderate to severe keratoconjunctivitis sicca	135	0.3% HPMC	0.4% hyaluronic acid	2 months
Johnson 2008 Randomized, parallel-group, controlled trial	Moderate dry eye	65	0.3% carbomer 934 (Lacryvisc)	0.18% sodium hyaluronate (Vismed)	1 month
Khanal 2007 Randomized, parallel-group, controlled trial	Mild to moderate dry eye	53	1.25% castor oil	0.32% HPMC (Artelac Single Dose Unit)	1 month
Kislan 2008 Randomized, crossover, controlled trial	Dry eye	80	PEG 400	HP-guar	1 and 2 months

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Lanz 2006 Randomized, cross-over, controlled trial	Moderate to severe dry eye	NR	0.3% HPMC (GenAqua®)		0.3% HPMC (Tears Naturale® Single Dose Unit)		4 weeks each phase
Lee 2011 Randomized, parallel-group, controlled trial	Mild to moderate dry eye	67	0.5% CMC (Refresh Plus)		0.1% sodium hyaluronate (Hynex)		2 months
Marner 1996 Randomized, cross-over, controlled trial	Dry eye	61	Carbomer-containing viscous gel (Lubrithal®)		1.4% PVA (Lacril®/Liquifilm®)		2 weeks each phase
Nelson 1988 Randomized, parallel-group, controlled trial	Moderately severe kerato-conjunctivitis sicca	36	1.4% PVA		0.1% sodium hyaluronate		2 months
Pinto-Bonilla 2015 Randomized, cross-over, controlled trial	Moderate to severe dry eye	17	Trehalose and hyaluronic acid (Thealoz Duo®)		PEG/PG/HP-guar (Systane®)		7 days
Simmons 2004a Randomized, parallel-group, controlled trial	Moderate to severe dry eye	NR	0.5% CMC (Refresh Plus®/ Celufresh®)	0.3% HPMC (Bion Tears®)	0.2% carbomer 980 gel (Viscotears Gel®)	0.3% HPMC (Polytears Free®)	1, 2, 4, 8, and 12 weeks
Simmons 2007 Randomized, parallel-group, controlled trial	Mild to moderate dry eye	103	0.5% CMC (Refresh Tears)		1.0% CMC (Refresh Liquigel)		7 and 30 days
Simmons 2015a	Dry eye	315	CMC-based artificial	CMC-based artificial tear (Refresh Optive® Sensitive), unit-dose	CMC-based artificial tear (Refresh Optive® Advanced Sensitive), multi-dose	CMC-based artifi-	7 and 30 days

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Randomized, parallel-group, controlled trial			tear (Refresh Optive® Advanced Sensitive), unit-dose		cial tear (Refresh Optive® Sensitive), multi-dose	
Simmons 2015b Randomized, parallel-group, controlled trial	Dry eye	305	CMC-based artificial tear (Optive Fusion)	CMC-based artificial tear, unspecified	0.5% CMC (Refresh Tears®)	3 months
Sullivan 1997 Randomized, parallel-group, controlled trial	Moderate to severe dry eye	123	0.3% carbomer ophthalmic gel 940 (Carbopol 934P)	Placebo (mannitol vehicle)		10, 21, 42, and 56 days
Tomlinson 2013 Randomized, crossover, controlled trial	Dry eye including mild dry eye	19	0.5% CMC (Refresh Tears®)	0.5% CMC/castor oil (Optive Plus™)	1.0% glycerin/castor oil (Refresh Ultra®)	2 weeks in each phase
Waduthantri 2012 Randomized, parallel-group, controlled trial	Dry eye	30	0.5% CMC (Refresh Tears®)	0.4% PEG 400/0.3% PG/HP-guar (Systane® Ultra)		1, 3, and 6 weeks
Wang 2007 Randomized, parallel-group, controlled trial	Dry eyes with grade II severity	80	0.2% carbomer (Vidisic Ophthalmic Gel)	0.32% HPMC (Artelac Ophthalmic Solution)		2 and 4 weeks
Wang 2010 Randomized, parallel-group, controlled trial	Dry eye	30	0.2% carbomer (Liposic® Ophthalmic Liquid Gel)	HP-guar (Systane® Lubricant Eye Drops)		2 and 4 weeks
Xiao 2008	Dry eye	60	0.4% carbomer-based gel	1.0% CMC-based artificial tear		3 months

Table 2. Summary of study design, study participants, interventions, and follow-up periods *(Continued)*

Cluster- randomized, parallel-group, controlled trial	

CMC: carboxymethylcellulose
HP: hydroxypropyl
HPMC: hydroxypropyl methylcellulose
PAA: polyacrylic acid
PEG: polyethylene glycol
PG: propylene glycol
PVA: polyvinyl alcohol

Table 3. Summary of interventions and comparisons

Comparison	Intervention	Comparison	Trial(s)
1. a)	0.3% carbomer	Placebo (saline or vehicle)	Baeyens 2012; Sullivan 1997
1. b)	0.5% CMC		Bruix 2006
1. c)	0.6% PG		Aguilar 2014
2	PEG + PG + HP-guar	0.5% or 1.0% CMC	Benelli 2010; Christensen 2004; Christensen 2009; Cohen 2014; Davitt 2010; Waduthantri 2012
3	0.4% PEG + 0.3% PG	0.3% HPMC (right eye)/0.5% CMC (left eye)	Comez 2013
4		0.25% PEG 400	Huth 2008
5	0.25% PEG 400	1% CMC	Dumbleton 2009
6		0.3% HPMC	Garcia-Lazaro 2011
7	PEG 400	HP-guar	Kislan 2008
8	0.5% CMC	0.1% or 0.2% sodium hyaluronate	Barabino 2014; Baudouin 2012; Lee 2011
9		0.3% HPMC	Donshik 1998 Trial 2; Donshik 1998 Trial 3; Simmons 2004a
10		1% CMC	Simmons 2007
11		CMC (lipid- versus aqueous-based)	Simmons 2015a
12		CMC + hyaluronic acid formulations	Simmons 2015b
13		0.5% CMC + castor oil	Tomlinson 2013
		1.0% glycerine + castor oil	
14	1% CMC	0.18% sodium hyaluronate	Brignole 2005
15		0.3% HPMC	Boisjoly 2003; Grene 1992
16		0.4% carbomer	Xiao 2008
17	0.2% carbomer	0.3% HPMC	Wang 2007
		0.3% lanolin	
18		HP-guar	Wang 2010
19	0.3% carbomer	0.18% sodium hyaluronate	Baeyens 2012; Johnson 2008
20		Carbomer (comparing different preservatives)	Bron 1998a

Table 3. Summary of interventions and comparisons *(Continued)*

21	0.2% PAA	1.4% PVA	Brodwall 1997; Bron 1998b; Foley-Nolan 1995
22	1.4% PVA	0.1% sodium hyaluronate	Nelson 1988
23		Carbomer, concentration unspecified	Marner 1996
24	0.3% HPMC	0.4% hyaluronic acid	Iester 2000
25		0.3% HPMC (with versus without bicarbonate)	Donshik 1998 Trial 1
26		0.3% HPMC (GenTeal versus Tears Naturale)	Lanz 2006
27		1.25% castor oil	Khanal 2007
28	Trehalose and hyaluronic acid	PEG + PG + HP-guar	Pinto-Bonilla 2015

CMC: carboxymethylcellulose
HP: hydroxypropyl
HPMC: hydroxypropyl methylcellulose
PAA: polyacrylic acid
PEG: polyethylene glycol
PG: propylene glycol
PVA: polyvinyl alcohol

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Dry Eye Syndromes
#2 dry near eye*
#3 ocular near dry*
#4 MeSH descriptor Tears
#5 tear*
#6 MeSH descriptor Xerophthalmia
#7 xerophthalmi*
#8 MeSH descriptor Vitamin A Deficiency
#9 Vitamin A deficien*
#10 MeSH descriptor Keratoconjunctivitis Sicca
#11 keratoconjunctivi*
#12 MeSH descriptor Sjogren's Syndrome
#13 sjogren* near syndrome
#14 MeSH descriptor Stevens-Johnson Syndrome
#15 steven* johnson syndrome*
#16 MeSH descriptor Pemphigoid, Benign Mucous Membrane
#17 cicatricial pemphgoid*
#18 blepharoconjunctiviti*
#19 MeSH descriptor Meibomian Glands
#20 meibomian
#21 MeSH descriptor Lacrimal Apparatus Diseases
#22 lacrimal
#23 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#24 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#25 (#23 OR #24)

#26 MeSH descriptor Nonprescription Drugs
#27 Over-the-counter
#28 OTC
#29 non-prescription-drug*
#30 MeSH descriptor Ophthalmic Solutions
#31 artificial tears
#32 MeSH descriptor Ointments
#33 ointment* or lubricant*
#34 MeSH descriptor Emollients
#35 demulcent* or emollient*
#36 MeSH descriptor Hyaluronic Acid
#37 sodium hyaluronate
#38 MeSH descriptor Polyvinyls
#39 polyvinyl alcohol
#40 polyvinylalcohol or povidone
#41 Propylene Glycol
#42 MeSH descriptor Polyethylene Glycols
#43 MeSH descriptor Methylcellulose
#44 hydroxypropyl*
#45 carbomer* or cellulose
#46 (castor or mineral) NEAR/2 oil*
#47 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46)
#48 (#25 AND #47)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp dry eye syndromes/
14. (dry adj2 eye$).tw.
15. (ocular adj2 dry$).tw.
16. exp tears/
17. tear$.tw.
18. exp xerophthalmia/
19. xerophthalmi$.tw.
20. exp vitamin A deficiency/
21. vitamin A deficien$.tw.
22. exp keratoconjunctivitis sicca/
23. keratoconjunctiviti$.tw.
24. exp Sjogren's syndrome/
25. Sjogren$ syndrome.tw.
26. exp Stevens Johnson syndrome/
27. Steven$ Johnson syndrome$.tw.
28. exp Pemphigoid, Benign Mucous Membrane/
29. cicatricial pemphigoid$.tw.
30. blepharoconjunctiviti$.tw.
31. exp meibomian glands/
32. meibomian.tw.
33. exp lacrimal apparatus diseases/
34. lacrimal.tw.
35. or/13-34

36. exp Nonprescription Drugs/
37. Over-the-counter.tw.
38. OTC.tw.
39. non-prescription-drug$.tw.
40. Ophthalmic Solutions/
41. artificial tears.tw.
42. Ointments/
43. (ointment$ or lubricant$).tw.
44. exp Emollients/
45. (demulcent$ or emollient$).tw.
46. Hyaluronic Acid/
47. sodium hyaluronate.tw.
48. exp Polyvinyls/
49. polyvinyl alcohol.tw.
50. (polyvinylalcohol or povidone).tw.
51. Propylene Glycol/
52. exp Polyethylene Glycols/
53. exp Cellulose/
54. hydroxypropyl$.tw.
55. (carbomer$ or cellulose).tw.
56. ((castor or mineral) adj2 oil$).tw.
57. or/36-56
58. 35 and 57
59. 12 and 58

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp dry eye/

34. (dry adj2 eye$).tw.
35. (ocular adj2 dry$).tw.
36. exp lacrimal fluid/
37. tear$.tw.
38. exp xerophthalmia/
39. xerophthalmi$.tw.
40. exp Retinol deficiency/
41. vitamin A deficien$.tw.
42. exp keratoconjunctivitis sicca/
43. keratoconjunctiviti$.tw.
44. exp Sjogren syndrome/
45. Sjogren$ syndrome.tw.
46. exp Stevens Johnson syndrome/
47. Steven$ Johnson syndrome$.tw.
48. exp Bullous skin disease/
49. cicatricial pemphigoid$.tw.
50. blepharoconjunctiviti$.tw.
51. exp meibomian gland/
52. meibomian.tw.
53. exp lacrimal apparatus/
54. exp lacrimal fluid/
55. lacrimal.tw.
56. or/33-55
57. non prescription drug/
58. Over-the-counter.tw.
59. OTC.tw.
60. non-prescription-drug$.tw.
61. eye drops/
62. artificial tear/
63. artificial tears.tw.
64. eye ointment/
65. (ointment$ or lubricant$).tw.
66. emollient agent/
67. (demulcent$ or emollient$).tw.
68. hyaluronic acid/
69. sodium hyaluronate.tw.
70. polyvinyl alcohol/
71. povidone/
72. polyvinyl alcohol.tw.
73. (polyvinylalcohol or povidone).tw.
74. propylene glycol/
75. macrogol derivative/
76. cellulose/
77. hydroxypropyl$.tw.
78. (carbomer$ or cellulose).tw.
79. ((castor or mineral) adj2 oil$).tw.
80. or/57-79
81. 56 and 80
82. 32 and 81

Appendix 4. LILACS search strategy

dry eye or Sjogren$ and Over the counter or OTC or non prescription or ophthalmic solution or artificial tears

Appendix 5. ISRCTN search strategy

(Condition: dry eye OR Sjogrens AND Interventions: Over the counter OR OTC OR non prescription OR ophthalmic solution OR artificial tears)

Appendix 6. ClinicalTrials.gov search strategy

(dry eye OR Sjogrens) AND (Over the counter OR OTC OR non prescription OR ophthalmic solution OR artificial tears)

Appendix 7. ICTRP search strategy

Condition = dry eye OR Sjogrens AND Intervention = Over the counter OR OTC OR non prescription OR ophthalmic solution OR artificial tears

Appendix 8. FDA search strategy

dry eye syndrome OR Sjogrens AND random OR randomly OR randomised OR randomized

CONTRIBUTIONS OF AUTHORS

JJN conceived the topic for review and further refined the specific interventions to be considered, with help from MM and ADP.
ADP and MM developed the protocol with input from JJN.
All three protocol authors responded to editorial and peer-review comments prior to publication of the protocol.

ADP and SMN extracted all data and wrote the first draft of the review.
All three review authors edited the manuscript and responded to peer-review comments prior to publication of the review.

DECLARATIONS OF INTEREST

ADP has received research support from Johnson & Johnson Vision Care and Oculus within the last three years; this funding is unrelated to the research discussed within this review.
SMN: none known.
JJN: none known.

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review had one significant difference between the protocol and review: we had intended to evaluate ingredients as described by the different FDA categories; however, we have ended up comparing specific ingredients and ignoring these categories. We made this change because of the great variation in artificial tears found in the literature search.

Our protocol did not include methods to prepare a "Summary of findings" table or assess the overall quality of evidence, as the protocol was published before this requirement was introduced (Pucker 2012). Although not specified in the protocol, we excluded studies in which the follow-up period was less than one week because our review aimed to investigate longer term outcomes. We decided during the screening process to include trials in which the age of participants was not reported; thus, some participants included in this review may not be adults as specified in the protocol. We intended to search the Science Citation Index for additional trials; however, due the large number of included trials and other sources searched, we did not search the Science Citation Index for this version of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acrylic Resins [administration & dosage]; Dry Eye Syndromes [*drug therapy]; Lubricant Eye Drops [*administration & dosage] [chemistry]; Nonprescription Drugs [administration & dosage] [chemistry]; Polyvinyl Alcohol [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans