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# Topical corticosteroids for dry eye (Review)

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[Intervention Review]

# Topical corticosteroids for dry eye

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## ABSTRACT

### Background

Dry eye disease (DED), arising from various etiologic factors, leads to tear film instability, ocular surface damage, and neurosensory changes. DED causes symptoms such as ocular dryness, burning, itching, pain, and visual impairment. Given their well-established anti-inflammatory effects, topical steroid preparations have been widely used as a short-term treatment option for DED. Because of potential risks of ocular hypertension, cataracts, and infections associated with the long-term use of topical steroids, published trials comparing the efficacy and safety of topical steroids (versus placebo) have mostly been of short duration (three to eight weeks).

### Objectives

To evaluate the effectiveness and safety of topical corticosteroids compared with no treatment, placebo, other steroidal or non-steroidal therapies, or a combination of therapies for DED.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, which contains the Cochrane Eyes and Vision Trials Register; 2021, Issue 8); Ovid MEDLINE; Ovid Embase; Latin American and Caribbean Health Sciences database (LILACS); ClinicalTrials.gov; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), without restriction on language or year of publication. The date of the last search was 20 August 2021.

### Selection criteria

We included randomized controlled trials (RCTs) in which topical corticosteroids, alone or in combination with tobramycin, were compared with no treatment, artificial tears (AT), vehicles, AT plus tobramycin, or cyclosporine A (CsA).

### Data collection and analysis

We applied standard Cochrane methodology.

### Main results

We identified 22 RCTs conducted in the USA, Italy, Spain, China, South Korea, and India. These RCTs reported outcome data from a total of 4169 participants with DED.

### Study characteristics and risk of bias

All trials recruited adults aged 18 years or older, except one trial that enrolled children and adolescents aged between 3 and 14 years. Half of these trials involved predominantly female participants (median 79%, interquartile range [IQR] 76% to 80%). On average, each trial enrolled 86 participants (IQR 40 to 158). The treatment duration of topical steroids ranged between one week and three months; trial duration lasted between one week and six months. Eight trials were sponsored exclusively by industry, and four trials were co-sponsored by industry and institutional or governmental funds. We assessed the risk of bias of both subjective and objective outcomes using RoB 2, finding nearly half of the trials to be at high risk of bias associated with selective outcome reporting.

**Findings**

Of the 22 trials, 16 evaluated effects of topical steroids, alone or in combination with tobramycin, as compared with lubricants (AT, vehicle), AT plus tobramycin, or no treatment. Corticosteroids probably have a small to moderate effect on improving patient-reported symptoms by 0.29 standardized mean difference (SMD) (95% confidence interval [CI] 0.16 to 0.42) as compared with lubricants (moderate certainty evidence). Topical steroids also likely have a small to moderate effect on lowering corneal staining scores by 0.4 SMDs (95% CI 0.18 to 0.62) (moderate certainty evidence). However, steroids may increase tear film break-up time (TBUT) slightly (mean difference [MD] 0.70 s, 95% CI 0.06 to 1.34; low certainty evidence) but not tear osmolarity (MD 1.60 mOsm/kg, 95% CI −10.47 to 13.67; very low certainty evidence).

Six trials examined topical steroids, either alone or in combination with CsA, against CsA alone. Low certainty evidence indicates that steroid-based interventions may have a small to moderate effect on improving participants' symptoms (SMD −0.33, 95% CI −0.51 to −0.15), but little to no effect on corneal staining scores (SMD 0.05, 95% CI −0.25 to 0.35) as compared with CsA. The effect of topical steroids compared to CsA alone on TBUT (MD 0.37 s, 95% CI −0.13 to 0.87) or tear osmolarity (MD 5.80 mOsm/kg, 95% CI −0.94 to 12.54; loteprednol etabonate alone) is uncertain because the certainty of the evidence is low or very low. None of the included trials reported on quality of life scores.

**Adverse effects**

The evidence for adverse ocular effects of topical corticosteroids is very uncertain. Topical corticosteroids may increase participants' risk of intraocular pressure (IOP) elevation (risk ratio [RR] 5.96, 95% CI 1.30 to 27.38) as compared with lubricants. However, when compared with CsA, steroids alone or combined with CsA may decrease or increase IOP elevation (RR 1.45, 95% CI 0.25 to 8.33). It is also uncertain whether topical steroids may increase risk of cataract formation when compared with lubricants (RR 0.34, 95% CI 0.01 to 8.22), given the short-term use and study duration (four weeks or less) to observe longer-term adverse effects.

**Authors' conclusions**

Overall, the evidence for the specified review outcomes was of moderate to very low certainty, mostly due to high risk of bias associated with selective results reporting. For dry eye patients whose symptoms require anti-inflammatory control, topical corticosteroids probably provide small to moderate degrees of symptom relief beyond lubricants, and may provide small to moderate degrees of symptom relief beyond CsA. However, the current evidence is less certain about the effects of steroids on improved tear film quality or quantity. The available evidence is also very uncertain regarding the adverse effects of topical corticosteroids on IOP elevation or cataract formation or progression. Future trials should generate high certainty evidence to inform physicians and patients of the optimal treatment strategies with topical corticosteroids in terms of regimen (types, formulations, dosages), duration, and its time-dependent adverse profile.

## PLAIN LANGUAGE SUMMARY

### What are the benefits and harms of topical corticosteroids for treating dry eye?

**What is dry eye?**

Dry eye is a common condition that occurs when a person's tears cannot lubricate their eyes sufficiently. Tears can be inadequate and unstable for many reasons. For example, dry eye may occur when tear production is reduced or when the tear quality is poor. This tear instability leads to inflammation and damage of the eye's surface. Dry eye is uncomfortable. People with dry eye often feel stinging or burning and sometimes experience blurred vision.

**How is it treated?**

Many treatment options are available for dry eye. For dry eye caused by the relative lack of the water layer in tears, treatments may include artificial tears, tear stimulants, serum eye drops, and punctal plugs. For dry eye caused by the blocked secretion of the lipid layer in tears, treatment options may include topical antibiotics, warm compresses, and anti-inflammatory agents, such as corticosteroids and cyclosporine A. Corticosteroids eye drops aim to reduce the inflammatory process and provide symptom relief with short-term use. High eye pressure and cataract formation are common concerns with longer-term use of corticosteroids.

**What did we want to find out?**

We evaluated whether corticosteroids eye drops, alone or in combination with other medications, can improve dry eye symptoms or test results used to diagnose or monitor dry eye. We also examined whether corticosteroids eye drops cause any unwanted effects on the eyes.

**What we did**

We conducted a systematic review. We searched for studies that compared corticosteroids eye drops with lubricating controls, other active treatment, or no treatment. We summarized these study findings and rated the evidence based on numbers of study participants and methods used in the studies.

**What we found**

We identified 22 clinical trials that enrolled a total of 4169 participants with dry eye. Most trials involved adults with a mean age between 50 and 67 years, except for one trial that exclusively involved children aged 3 to 14 years. Treatment duration ranged between 7 days and 3 months. When compared with lubricants, such as artificial tears, or with cyclosporine A, corticosteroids eye drops were probably effective in improving patient-reported symptoms and clinical tests, such as corneal staining. Clinicians may use corneal staining as a test for cornea damage. However, corticosteroids eye drops may result in little to no difference in tear quality or quantity. At the same time, it is uncertain whether steroid use may increase or decrease the chance of increased eye pressure, new cataract formation, or worsening of an existing cataract.

**What are the limitations of the evidence?**

More than half of the included trials had flawed study methods or did not report their results fully. These deficiencies led to concerns about the study findings and decreased our confidence in the evidence generated in this systematic review.

**How up-to-date is this evidence?**

The evidence is up-to-date as of August 2021.

## SUMMARY OF FINDINGS

### Summary of findings 1. Steroids compared with lubricants

**Steroid treatment compared with lubricant (artificial tears alone or with tobramycin, vehicle, or no treatment) for dry eye**

**Patient or population:** people with dry eye

**Setting:** eye clinics or medical centers

**Intervention:** steroid alone (clobetasone, difluprednate, loteprednol etabonate, fluorometholone, corticosteroid) or in combination with tobramycin

**Comparison:** artificial tears (including hyaluronate, PVP, Soothe Emollient), vehicle, no treatment, or artificial tears with tobramycin

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk Artificial tears | Corresponding risk Steroid intervention | | | | |
| **Change in patient-reported symptom scores** (lower is favored) | Change in symptom scores in the steroid groups was on average 0.29 SMD (95% CI 0.16 to 0.42) lower than in the artificial tears groups. | | **SMD −0.29** (95% CI −0.42 to −0.16) | 3654 (15) | ⊕⊕⊕⊖ **Moderate**[1] | As suggested in Cohen 1988, 0.2 SMD represents a small difference, and 0.5 a moderate difference. |
| **Change in patient-reported quality of life scores** | No studies measured this outcome. | | - | - | - | |
| **Change in TBUT (seconds)** (longer is favored) | Change in TBUT in the steroid groups was on average 0.70 (95% CI 0.06 to 1.34) longer than in the artificial tears groups. | | **MD 0.70** (95% CI 0.06 to 1.34) | 587 (7) | ⊕⊕⊖⊖ **Low**[1,2] | MID 5 s (Wolffsohn 2017) |
| **Change in fluorescein corneal staining scores** (lower is favored) | Change in fluorescein corneal staining scores in the steroid groups was on average 0.40 SMD (95% CI 0.18 to 0.62) lower than in the artificial tears groups. | | **SMD −0.40** (95% CI −0.62 to −0.18) | 3583 (15) | ⊕⊕⊕⊖ **Moderate**[1] | As suggested in Cohen 1988, 0.2 SMD represents a small difference, and 0.5 a moderate difference. |
| **Change in tear osmolarity (mOsm/kg)** | 336.9 (SD 22.23) | 338.5 (SD 15.81) | **MD 1.60** | 40 (1) | ⊕⊖⊖⊖ **Very low**[3,4] | MID 5 mOsm/L (Wolffsohn 2017) |

| | | | | | |
|---|---|---|---|---|---|
| (lower is favored) | | | (95% CI −10.47 to 13.67) | | |
| **Adverse effect:**<br>**incident elevated IOP**<br>(follow-up 14 days to 2 months) | 9 incidents<br>per 10,000 participants | 54 incidents (95% CI 12 to 246)<br>per 10,000 participants | **RR 5.96**<br>(95% CI 1.30 to 27.38) | 2264 (8) | ⊕⊖⊖⊖<br>**Very low**[3,4] |
| **Adverse effect:**<br>**new cataract formation**<br>(follow-up 14 days to 4 weeks) | 16 incidents<br>per 10,000 participants | 5 incidents (95% CI 0.2 to 132)<br>per 10,000 participants | **RR 0.34**<br>(95% CI 0.01 to 8.22) | 1205 (3) | ⊕⊖⊖⊖<br>**Very low**[3,4] |

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and the associated 95% CI).

**CI,** confidence interval; **IOP,** intraocular pressure; **MD**, mean difference; **MID**, minimally important difference; **mOsm**, milliosmoles; **PVP,** polyvinylpyrrolidone; **RR**, risk ratio; **SD**, standard deviations; **SMD**, standardized mean difference; **TBUT**, tear film break-up time

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded for risk of bias (−1).
[2] Downgraded for unexplained heterogeneity (−1).
[3] Downgraded for imprecision (−1).
[4] Downgraded for high risk of bias (−2).

### Summary of findings 2. Steroids compared with cyclosporine A

| **Steroid alone or in combination treatment compared with cyclosporine A for dry eye** |
|---|
| **Patient or population:** people with dry eye |
| **Setting:** eye clinics or medical centers |
| **Intervention:** steroid alone (fluorometholone, loteprednol etabonate, methylprednisolone) or in combination with cyclosporine A |
| **Comparison:** cyclosporine A |

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk Cyclosporine A | Corresponding risk Steroid intervention | | | | |
| **Change in patient-reported symptom scores** (lower is favored) | Change in symptom scores in the steroid groups was on average 0.33 SMD (0.15 to 0.51) lower than in the cyclosporine A groups. | | **SMD −0.33** (95% CI −0.51 to −0.15) | 465 (6) | ⊕⊕⊖⊖ **Low**[1,2] | As suggested in Cohen 1988, 0.2 SMD represents a small difference, and 0.5 a moderate difference. |
| **Change in patient-reported quality of life scores** | No studies measured this outcome. | | - | - | - | |
| **Change in TBUT (seconds)** (longer is favored) | Change in TBUT in the steroid groups was on average 0.37 longer (0.13 shorter to 0.87 longer) than in the cyclosporine A groups. | | **MD 0.37** (95% CI −0.13 to 0.87) | 353 (5) | ⊕⊕⊖⊖ **Low**[1,2] | MID 5 s (Wolffsohn 2017) |
| **Change in fluorescein corneal staining scores** (lower is favored) | Change in fluorescein corneal staining scores in the steroid groups was on average 0.05 SMD higher (0.25 lower to 0.35 higher) than in the cyclosporine A groups. | | **SMD 0.05** (95% CI −0.25 to 0.35) | 465 (6) | ⊕⊕⊖⊖ **Low**[1,2] | As suggested in Cohen 1988, 0.2 SMD represents a small difference, and 0.5 a moderate difference. |
| **Change in tear osmolarity (mOsm/kg)** (lower is favored) | 1.50 lower (SD 17.33) | **LE alone:** 4.30 higher (2.44 lower to 11.04 higher) | **MD 5.80** (95% CI −0.94 to 12.54) | 69 (1) | ⊕⊖⊖⊖ **Very low**[2,3] | MID 5 mOsm/L (Wolffsohn 2017) |
| | | **LE + CsA:** 2.20 higher (6.00 lower to 10.4 higher) | **MD 2.20** (95% CI −6.00 to 10.4) | 66 (1) | | |
| **Adverse effect: incident elevated IOP** (follow-up 8 weeks to 6 months) | 12 incidents per 1000 participants | 17 incidents (3 to 100) per 1000 participants | **RR 1.45** (95% CI 0.25 to 8.33) | 331 (4) | ⊕⊖⊖⊖ **Very low**[2,3] | The duration of steroid use ranged from 3 weeks to 3 months. |
| **Adverse effect:** | No studies measured this outcome. | | - | - | - | |

| | |
|---|---|
| **new cataract formation** | |

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and the associated 95% CI).

**CI,** confidence interval; **CsA,** cyclosporine A; **IOP,** intraocular pressure; **LE,** loteprednol etabonate; **MD**, mean difference; **MID**, minimally important difference; **mOsm**, milliosmoles; **RR**, risk ratio; **SD**, standard deviations; **SMD**, standardized mean difference; **TBUT**, tear film break-up time

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded for risk of bias (−1).
[2] Downgraded for imprecision (−1).
[3] Downgraded for high risk of bias (−2).

# BACKGROUND

## Description of the condition

Dry eye disease (DED), arising from various etiologic factors, leads to tear film instability, ocular surface damage, and neurosensory changes (Bron 2017). DED causes symptoms such as ocular dryness, burning, itching, pain, and visual impairment (Messmer 2015). There was a lack of consensus in disease definition before 2017, and prevalence estimates of symptomatic DED varied widely between 5% and 50% (Stapleton 2017). In a recent cross-sectional survey on 16 selected towns in Palestine's northern West Bank, Shanti and colleagues reported that 64% of the study population fulfilled the diagnostic criteria for DED (Shanti 2020). Yu and colleagues estimated the average annual healthcare cost for a patient with DED in the USA to be USD 783, and the overall cost of DED to the healthcare system to be USD 3840 million (Yu 2011). It is estimated that patients with DED in the UK spent USD 1.10 million (2003/2004 prices) seeking ophthalmologic care, with nearly 50% of the cost attributable to prescription drugs (Nichols 2016). Although older age and female sex are consistent risk factors for DED, the pathophysiological mechanisms underlying these correlations remain unclear (Nelson 2017). Besides environmental predispositions (low humidity, high temperature, windy conditions) (Bron 2017), other well-characterized risk factors include prolonged screen time, contact lens wearing, androgen deficiency, medication use, and surgical and cosmetic procedures (Gomes 2017; Stapleton 2017).

To guide clinical management, DED has been categorized historically into aqueous-deficient (due to tear insufficiency) and evaporative (due to increased tear evaporation) subtypes (Messmer 2015). Sjögren syndrome is a major underlying contributor to aqueous-deficient dry eye. Meibomian gland diseases, including meibomian gland dysfunction (MGD) and ocular surface-related causes, can lead to evaporative dry eye (Bron 2017).

Differentiating between aqueous-deficient dry eye, evaporative dry eye, and a mixed mechanism comprised of both subtypes is crucial for guiding treatment plans (Bron 2017; Jones 2017). For aqueous-deficient dry eye, treatment options comprise tear supplements, tear stimulants, and, in more severe cases, punctal plugs to preserve tears. Recent systematic reviews have demonstrated the safety and efficacy of artificial tears (Pucker 2016), but not of punctal plugs, Ervin 2017, or autologous serum eye drops (Pan 2017). For evaporative dry eye, cause-specific therapies are available for various meibomian gland diseases, such as lid hygiene and topical antibiotics for anterior blepharitis (Jones 2017); warm compresses for meibomian gland dysfunction (Jones 2017); and anti-inflammatory agents, such as topical corticosteroids (steroids) (Jones 2017), cyclosporine A (De Paiva 2019), and rebamipide for ocular surface inflammation (Holland 2019; Kojima 2020).

## Description of the intervention

Given their well-established anti-inflammatory effects, topical steroid preparations have been widely used as a short-term treatment option for DED. Several trials have shown one-month use of topical steroid drops to improve symptoms and clinical signs (Avunduk 2003; Lee 2006; Pflugfelder 2004). The rapid onset of therapeutic effects of topical steroids could make them a useful pre-treatment (or induction) choice before initiating long-term cyclosporin (non-steroidal) treatment (Byun 2012; Sheppard 2014).

## How the intervention might work

Accumulating evidence has demonstrated the presence of pro-inflammatory cytokines and T helper cells in the ocular surface regardless of DED etiologies, suggesting that ocular inflammation is a key factor in DED pathophysiology (Bron 2017). Topical steroids have been shown to exert anti-inflammatory actions on multiple targets associated with DED symptoms and signs, including decreasing expression of cytokines, maintaining the integrity of corneal epithelium (De Paiva 2006a; De Paiva 2006b), and restoring tear production in animal models (Lekhanont 2007). In humans, topical steroids have been show to reduce pro-inflammatory cytokines in tears (Lekhanont 2007).

## Why it is important to do this review

Based on 2013 Medicare data, medications for DED ranked the second highest total costs generated by eye care (Newman-Casey 2018). In England, DED was reportedly a major contributor to prescription costs by general practitioners in the National Health Service (Stephenson 2016). Within the ophthalmic medication group of ocular inflammation medications, prednisolone acetate was the most commonly prescribed ocular anti-inflammatory drug by volume and cost (Newman-Casey 2018). Despite widespread use of topical steroids clinically, significant debates about their role in DED remain. Because of potential risks of ocular hypertension, cataracts, and infections associated with the long-term use of topical steroids, published trials comparing the efficacy and safety of topical steroids (versus placebo) in individuals with DED have mostly been of short duration (three to eight weeks) (Jones 2017). Heterogeneity in outcome measures, patient populations, and follow-up durations, albeit short, suggests that the evidence supporting the routine use of topical steroids for DED may not be robust. In large surveys that we conducted, clinicians treating patients with dry eye prioritized the effectiveness of topical anti-inflammatory treatments (such as corticosteroids) as the most important unanswered question (Saldanha 2017), and patients prioritized it as the third-most important question (Saldanha 2018).

A systematic review that critically appraises the currently available data on the effects of topical steroids will provide clinicians, patients, and policymakers with robust and updated research evidence for treating DED. Along with previously published Cochrane Reviews on other local treatments for DED (De Paiva 2019; Downie 2017; Ervin 2017; Pan 2017; Pucker 2016), the current review will inform physicians of the risk-benefit trade-offs for prescribing topical steroids, even for short-term use. The findings of the current review may also highlight evidence gaps and suggest potential directions for future research to address patient-important clinical outcomes.

# OBJECTIVES

To evaluate the effectiveness and safety of topical corticosteroids compared with no treatment, placebo, other steroidal or non-steroidal therapies, or a combination of therapies for DED.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We included randomized controlled trials (RCTs) only. We excluded within-person studies, where eyes were randomly allocated to the intervention and comparator, because we were mostly interested in outcomes at the individual rather than the eye level.

### Types of participants

We included RCTs that enrolled participants with clinically diagnosed DED regardless of etiology, or participants who reported dry eye symptoms regardless of severity. We excluded trials of patients with DED secondary to medications or medical procedures, because patients with iatrogenic DED likely shared a distinct profile of risk factors from those with primary DED.

### Types of interventions

We included trials comparing topical steroids with no treatment, placebo, artificial tears, other steroidal or non-steroidal therapy, or a combination of therapies. We planned to include trials that examined the following topical steroidal preparations.

- Betamethasone
- Clobetasone butyrate
- Dexamethasone
- Difluprednate
- Fluorometholone
- Loteprednol etabonate
- Prednisolone

We did not require a minimum treatment frequency or duration as an eligibility criterion.

### Types of outcome measures

#### *Critical outcomes*

- Improvement in patient-reported symptoms, quantified by patient questionnaires, such as the Ocular Surface Disease Index or other validated questionnaires (Schiffman 2000).
- Improvement in patient-reported general or vision-related quality of life, measured by patient questionnaires such as the Dry Eye-Related Quality of Life Score (DEQS).
- Change in visual function, quantified as differences in reading speed using tests such as the short-duration out-loud reading test (Legge 1989), the 30-minute sustained silent reading test, and the International Reading Speed Texts (IReST).
- Change in tear film stability (tear film break-up time [TBUT]).

We planned to collect outcomes at key time points that were short term (1 to 3 months), intermediate term (3 to < 6 months), or long term (≥ 6 months). All included trials had followed participants no longer than three months. For eligible studies that reported outcomes at multiple time points, we extracted outcome data, change scores, or post-treatment measures, reported at the longest follow-up time point.

#### *Important outcomes*

- Change in ocular surface staining (Rose Bengal score/Van Bijsterveld score, fluorescein dye, or Lissamine green dye).
- Proportion of participants who showed a decrease in tear osmolarity from baseline, or mean change in tear osmolarity (mOsm/kg).
- Change in aqueous tear production (Schirmer test score or Jones basal secretion test).

We collected these important outcomes at the same time points as for critical outcomes.

#### Adverse events

We collected the proportion of participants with any ocular complication, elevated intraocular pressure (≥ 21 mmHg), new cataract formation, or delayed or impaired wound healing. Because few trials reported these specific ocular adverse events separately, we also collected total numbers of ocular and total (ocular plus systemic) adverse events documented for each comparison group as reported by the included studies. We extracted data on adverse events reported at the longest time point provided in each included RCT.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (Issue 8, 2021), Ovid MEDLINE, Ovid MEDLINE E-pub Ahead of Print, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily (January 1946 to 20 August 2021), Embase (January 1947 to 20 August 2021), PubMed (1946 to 20 August 2021), Latin American and Caribbean Health Sciences Literature database (LILACS) (1982 to 20 August 2021), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic search for trials. Our last date of search was 20 August 2021.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), PubMed (Appendix 4), LILACS (Appendix 5), ClinicalTrials.gov (Appendix 6), and the WHO ICTRP (Appendix 7).

### Searching other resources

We manually searched the reference lists of included studies, review articles, and guidelines for additional eligible trials, but did not identify any. We did not handsearch conference proceedings or journals, as these are included in CENTRAL.

## Data collection and analysis

### Selection of studies

The Information Specialist provided separate search results from the electronic databases and the trial registries. We then applied the web-based review management software Covidence to automatically identify and remove duplicate references among the imported citations (Covidence). Two review authors worked in pairs to independently screen the titles and abstracts resulting from the searches using Covidence. Based on the eligibility criteria, each

review author classified each citation as 'relevant (yes),' 'maybe relevant,' or 'not relevant (no)' for subsequent full-text review. We then retrieved the full-text articles for the records classified as 'relevant' or 'maybe relevant.' Two review authors worked in pairs to independently assess the full-text records for eligibility as described in Criteria for considering studies for this review. Any disagreements were resolved by discussion.

We also contacted the investigators of potentially eligible studies to request additional information to determine the eligibility of studies as needed. If the study authors did not respond within two weeks, we used the information available from publications and trial registries to determine eligibility whenever feasible. We listed all excluded studies with the reasons for their exclusion in Characteristics of excluded studies. Regarding eligible studies identified on trials registers, we included any such studies in the review irrespective of whether we could identify or access published or unpublished data. In particular, we classified eligible trials as 'awaiting classification' if the trials were completed but no study results were publicly available, or 'ongoing' if the trials were not yet completed. Any discrepancies were resolved by discussion within the review author team.

### Data extraction and management

One review author (SL) extracted data using an online structured form developed by Cochrane Eyes and Vision (Covidence), and a second review author (TR) independently verified the data entered into Covidence. We contacted trial investigators or sponsors for missing data. If the trial investigators or sponsors did not respond within two weeks, we extracted the relevant data available to us from trials registers or clinical study reports and other regulatory documents. We imported adjudicated data into Review Manager Web (RevMan Web 2022), which was again verified by a second review author for accuracy.

We extracted the following information from each included study: trial setting, countries where participants were recruited, sample size, study duration, and other trial-level characteristics; participants' composition of age, sex, or major medical comorbidities; outcome data and adverse events. We collected continuous variables as mean, standard deviation or the associated 95% confidence intervals (95% CI), and dichotomous variables as number of participants for which the outcome was measured. In some studies, numerical data were only available in figures, from which we applied a free, web-based software to extract outcome data for meta-analysis (WebPlotDigitizer), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2021). For multi-arm studies, we only collected data relevant to our intervention and comparator groups. If two groups contained relevant data, we combined the groups using the calculator within Review Manager Web, or included each group in relevant meta-analyses separately in order to avoid double counting the comparator group.

### Assessment of risk of bias in included studies

Two review authors (SL and TR) independently assessed risk of bias using Cochrane's RoB 2 tool for two critical outcomes (Higgins 2021a). As prespecified in the protocol, we chose to apply the RoB 2 tool to patient-reported symptom scores and corneal fluorescein staining scores, as these two outcomes were the most frequently reported outcomes in the included trials. Any disagreements on the risk of bias assessments were resolved via discussion within the review author team.

We specifically considered and reported on the following domains.

- Bias arising from the randomization process
- Bias introduced by deviations from intended interventions
- Bias due to missing outcome data
- Bias in outcome measurement
- Bias in selective reporting of outcome data

We judged each domain for each study as low risk of bias, high risk of bias, or some concerns as guided by signaling questions in each domain. Overall, we assessed each trial as having:

- 'low risk of bias' if all domains were judged to be at low risk;
- 'some concerns' if one or more domains were judged to be with some concerns, and none were at high risk;
- 'high risk of bias' if one or more domains were considered as at high risk, or if multiple domains were judged to be with some concerns such that we had low confidence in the validity of the reported findings (Higgins 2021a).

### Measures of treatment effect

We calculated mean differences (MD) with 95% CI for continuous outcomes, and risk ratios (RR) with 95% CI for dichotomous outcomes. Where possible, we checked for the skewness of continuous data (Altman 1996). We used the standardized mean difference (SMD) for patient-reported symptom scores and corneal staining scores because not every trial utilized the same symptom questionnaire or staining scoring system. Interpretation of treatment effects expressed in units of SMD, such as patient-reported symptoms scores and fluorescein corneal staining scores, may follow the rule of thumb as suggested by Cohen, which considers an SMD of 0.2 a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988).

### Unit of analysis issues

In trials where individuals were randomly allocated to treatment, but only one eye per person was included in the trial, we documented how the eye was selected or how the investigators decided from which eye to report data. If participants were randomly allocated to treatment, and both eyes were included but reported separately, we chose to collect and analyze outcome data for the right eye, rather than analyzing data of both eyes as planned in the protocol (Differences between protocol and review). We excluded studies that allocated different eyes to different treatments, as there might be cross-over effects due to systemic absorption or biased reporting of patient-reported symptom scores for each eye.

### Dealing with missing data

We planned to use imputed data if computed by the trial investigators using an appropriate method; we did not plan to impute missing data ourselves. We contacted the trial investigators and requested clarification or missing information when the trial publication did not include outcome data for all randomized participants. If we did not hear back from the trial investigators within two weeks, we proceeded by conducting a complete-case analysis, assuming that the data were missing completely at random (Bhaskaran 2014). We assessed whether this assumption

was reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up and the reasons for loss to follow-up by treatment group, if reported.

### Assessment of heterogeneity

We examined the overall characteristics of the studies, in particular the types of participants, types of interventions, and study design, to assess the extent to which the studies were sufficiently similar to permit a meaningful meta-analysis for a given outcome. We considered the size and direction of intervention effects and took into account the amount of heterogeneity as quantified by the $I^2$ statistic (Higgins 2002). As suggested in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021), we used the following thresholds to interpret $I^2$ values:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

### Assessment of reporting biases

We assessed selective outcome reporting for each included trial as guided by relevant signaling questions in the RoB 2 tool (Higgins 2021a). In the protocol development stage, we planned to evaluate potential risk of bias arising from non-reporting (missing evidence) for the critical outcomes using the Risk of Bias due to Missing Evidence tool (ROB-ME, Page 2021). However, because the tool is still in its preliminary version, we decided not to perform this assessment for the current version of the review. We will assess the tool's availability in future updates of this review.

### Data synthesis

In addition to qualitative synthesis of the included trials, we combined data using a random-effects model as default if there were three or more trials reporting on the same outcome. When we judged the evidence as having considerable clinical, methodological, or statistical heterogeneity, we did not combine the data in a meta-analysis but instead described the data qualitatively.

### Subgroup analysis and investigation of heterogeneity

We planned that when there were sufficient trials (> 10), we would conduct subgroup analysis on critical outcomes by sex and etiology of dry eye (Sjögren syndrome, non-Sjögren syndrome, meibomian gland dysfunction), separately. Because few studies reported on TBUT, we performed post hoc subgroup analysis on fluorescein staining results by etiology of dry eye (Differences between protocol and review). To explore potential sources of heterogeneity, we also performed additional post hoc subgroup analyses on patient-reported symptoms and fluorescein staining scores by scoring system, source of trial funding, and intervention regimen (Differences between protocol and review).

### Sensitivity analysis

We performed sensitivity analyses for each critical outcome by excluding trials at high risk of bias for that particular outcome and by excluding industry-controlled studies.

### Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables presenting relative or absolute risks (Schünemann 2019). Two review authors independently graded the overall certainty of the evidence for each of the following outcomes using the GRADE approach (Schünemann 2013).

- Improvement in patient-reported symptom scores
- Improvement in patient-reported general or vision-related quality of life scores
- Improvement in TBUT
- Improvement in ocular surface staining
- Improvement in tear osmolarity
- Ocular adverse event: incident elevated intraocular pressure (IOP) ≥ 21 mmHg
- Ocular adverse event: new cataract formation

We graded the certainty of the evidence as 'high,' 'moderate,' 'low,' or 'very low' according to (1) risk of bias among the included trials; (2) indirectness of evidence; (3) unexplained heterogeneity or inconsistency of results; (4) low precision of results; and (5) risk of publication bias (Schünemann 2013). Any discrepancies between the two review authors were resolved by discussion.

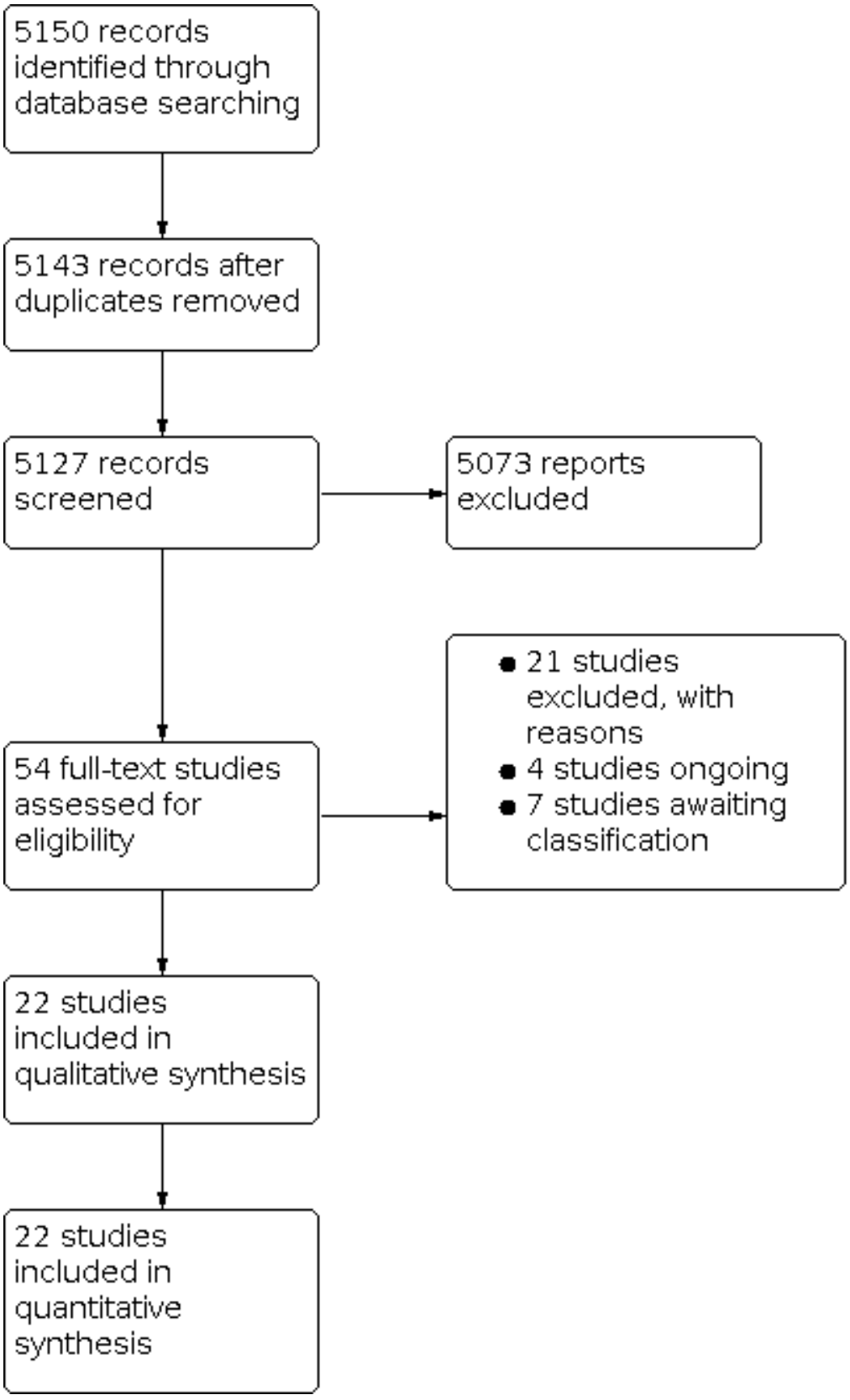
## RESULTS

## Description of studies

### Results of the search

We searched the electronic databases in August 2021, identifying 5143 records (5127 studies) after removal of duplicates. After excluding 5073 irrelevant records, we screened 54 full-text reports and included 22 studies in the review (Figure 1). We excluded 21 studies, with reasons for their exclusion reported in Characteristics of excluded studies, and assessed 4 studies as 'ongoing' (CTRI/2021/02/031182; ISRCTN16288419; NCT04734197; NCT04734210), and 7 studies as 'awaiting classification' (ChiCTR-IPR-15007196; Herman 2005; NCT00471419; NCT00560638; NCT01562795; NCT03418727; NTR2291).

**Figure 1. Study flow diagram.**



## Included studies

### *Types of studies*

All 22 included RCTs had a parallel-group design and compared topical corticosteroids alone or in combination versus lubricants or another pharmacological intervention in participants with dry eye. Eleven trials were conducted in the USA, nine in Asia (six in China, two in South Korea, one in India), and two in Europe (one each in Spain and Italy). The trials were published between 2003 and 2021. Twelve trials were registered on trial registries, but protocols were publicly available for only five trials (Akhlaq 2019; KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3)). Eleven trials provided power or sample size calculations for at least one study outcome.

Seven trials were multisite (KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223; Pflugfelder 2004; Sheppard 2014), while the rest were single-site trials conducted in university-affiliated medical centers. Eight trials had pharmaceutical sponsorship as the sole source of funding (36%) (Akhlaq 2019; Bausch 2013; KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223; Pflugfelder 2004). Another four trials reported dual funding sources from the industry and the affiliated institution or the government (18%) (Aragona 2013; Pinto-Fraga 2016; Qazi 2015; Sheppard 2014). Five trials were supported by either the investigators' affiliated institution, Byun 2012, or government funding (Avunduk 2003; Chen 2020; Lee 2014; Wan 2012). Authors of another four trials did not disclose any financial support (Cao 2018; Li 2021; Luo 2013; Singla 2019). Lin and colleagues reported receiving no funding and disclosed no conflicts of interest (Lin 2015).

Eighteen trials (82%) randomized the interventions at the participant level and reported the outcomes as such. Four trials randomized participants to the interventions but reported findings exclusively at the eye level (Li 2021; Sheppard 2014; Singla 2019; Wan 2012). Most trials randomized participants into two groups, except for four trials that randomized participants into three or more groups (Avunduk 2003; Bausch 2013; Luo 2013; Qazi 2015). Corticosteroid treatment durations ranged between one week and three months, and follow-up durations was generally short, ranging from one week to six months.

For details on the included trials, see Characteristics of included studies.

### *Types of participants*

The 22 included trials reported data for a total of 4169 participants, excluding those randomized to treatments that were irrelevant to the current review. Two trials did not report numbers of participants initially randomized, overall, or for each comparator group, but only reported those included for outcomes analyzed (Avunduk 2003; Sheppard 2014). On average, each trial enrolled (or reported data for) a median number of 86 participants (interquartile range [IQR] 40 to 158). All trials but one recruited adult participants aged 18 years or older, with the majority of trials enrolling middle-aged participants with mean ages ranging between 50 and 67 years. The exception was a trial that exclusively recruited children and adolescents aged between 3 and 14 years (Cao 2018).

In seven trials, both males and females were nearly equally represented, with females consisting of between 55% and 64% of trial populations (Avunduk 2003; Cao 2018; Lee 2014; Li 2021; Qazi 2015; Singla 2019; Wan 2012). However, in 11 trials, the investigators enrolled predominantly female participants (median 79%, IQR 76% to 80%; maximum 95%). Authors of another two trials did not report on sex distribution of the study participants (Akhlaq 2019; Lin 2015).

Five trials exclusively enrolled participants with Sjögren's, Aragona 2013; Lin 2015, or meibomian gland dysfunction (Lee 2014; Luo 2013; Qazi 2015); the other 17 trials did not report on the underlying etiologies of dry eye.

### *Types of interventions*

Topical corticosteroids were used as stand-alone or combination interventions in 18 and 4 trials, respectively. Treatment duration of the corticosteroid intervention ranged from one week to three months.

Of the 18 trials that evaluated corticosteroids alone, 12 used loteprednol etabonate (LE) 0.1% (Chen 2020), 0.25% (KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3)), or 0.5% (Akhlaq 2019; Bausch 2013; Lee 2014; Pflugfelder 2004; Qazi 2015; Wan 2012). Another trial also compared LE with hyaluronic acid (HA), but the authors did not report the drug concentration (Cao 2018). Six trials evaluated difluprednate 0.05% (Durezol) (NCT01276223), clobetasone butyrate (CB) 0.1% (Aragona 2013), or fluorometholone (FML) 0.1% (Li 2021; Lin 2015; Pinto-Fraga 2016). In Avunduk 2003, the intervention group also received FML, but its concentration was not reported.

Four trials evaluated topical corticosteroids in combination with either cyclosporine A (CsA) 0.05%, Byun 2012; Sheppard 2014; Singla 2019, or tobramycin (Luo 2013), in comparison with CsA. Corticosteroids in these combination interventions were LE 0.5% (Sheppard 2014; Singla 2019), methylprednisolone (MP) 1% (Byun 2012), and dexamethasone (DEXA, unspecified concentration) (Luo 2013). In addition to one intervention group with LE 0.5% treatment alone, investigators in two of the four three-arm trials also compared the combination effects of LE 0.5% plus CsA 0.05%, Bausch 2013, or LE 0.5% plus tobramycin (Qazi 2015). In four trials that combined topical corticosteroid with CsA, two trials evaluated the benefits of pre-treatment with corticosteroid for two weeks before initiating CsA treatment (Bausch 2013; Sheppard 2014); the other two trials evaluated the effects of concurrent initiation of topical corticosteroid and CsA treatment (Byun 2012; Singla 2019).

Comparator interventions included no treatment (Lee 2014), lubricating solutions, emollients, or gels, or another active therapy. We did not identify any true placebo-controlled trials when reviewing the literature, and we use 'lubricant' to reference all inert comparators that did not exhibit anti-inflammatory effects. These lubricants consisted of artificial tears (AT) in various formulations (Avunduk 2003; Qazi 2015), emollients (Akhlaq 2019), HA (Cao 2018; Chen 2020; Li 2021), and vehicle (Aragona 2013; KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223; Pflugfelder 2004; Pinto-Fraga 2016). We also considered a combination of AT and tobramycin as equivalent to a lubricating control when compared with DEXA plus tobramycin (Luo 2013).

Active therapies consisted of mostly topical CsA 0.5% (Bausch 2013; Byun 2012; Lin 2015; Sheppard 2014; Singla 2019; Wan 2012). In most active-controlled trials, participants in both groups were allowed to apply lubricants of the same formulation to study eyes during the study period, except in one study where participants in the comparison group received only CsA 0.5% (Byun 2012).

### *Types of outcomes*

We planned to evaluate the effects of topical corticosteroid on four critical outcomes and three important outcomes (Liu 2021). However, none of the included trials described patient-reported quality of life or change in visual function, two of our prespecified critical outcomes.

All trial investigators randomized and reported at the individual level, except for three trials that reported at the eye level (Sheppard 2014; Singla 2019; Wan 2012); we included only data from the right eyes in data analysis from these three trials. Another two study teams prespecified how they selected study eyes for outcome reporting (right eyes or the worst eyes) (Chen 2020; Lee 2014). In two trials, the authors did not specify the unit of analysis for outcomes reported (Cao 2018; Luo 2013); post hoc Student t-test results suggested that the unit of analysis might be eye, and the comparisons had accounted for within-person correlation.

### *Critical outcomes*

#### Change in patient-reported symptom scores

Twenty-one trials reported changes in patient-reported symptoms; the remaining trial only reported changes in ocular surface signs (Cao 2018). Change scores were provided by 6 of the 21 trials (Bausch 2013; KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223; Pflugfelder 2004). These change scores were analyzed together with post-treatment symptom scores from the other 15 trials, as suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b).

Thirteen trials used the Ocular Surface Disease Index (OSDI) (Akhlaq 2019; Bausch 2013; KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); Lee 2014; Li 2021; Lin 2015; Pinto-Fraga 2016; Qazi 2015; Sheppard 2014; Singla 2019), in which participants were asked to rate different aspects of their symptom severity on a scale of 0 to 4; the total score ranged from 0 to 100 (Schiffman 2000).

Aragona 2013 and Pflugfelder 2004 applied visual analogue scales (VAS, 0 to 100 points) to document participants' symptoms: burning/stinging, itching, grittiness/scratchiness/foreign body sensation, photophobia/blurred vision, sticky eye, and dryness/tired eye sensation. In a separate trial (NCT01276223), the investigators also used VAS to record symptom severity and frequency, scored each from 0 to 100, and reported the composite score ranging up to 200.

Chen 2020 used the Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire, an 8-item questionnaire with scores of 0 to 3 for each item (Ngo 2013), but the authors assessed only dryness, foreign body sensation, burning sensation, and eye irritation, with a maximum score of 12.

Avunduk 2003 used the Dry Eye Screening Questionnaire (DESQ), a 14-item instrument (each with a 4-point scale) developed for screening purposes (Oden 1998).

Three trials did not report on the specific questionnaires used for symptoms (Byun 2012; Luo 2013; Wan 2012).

#### Improvement in patient-reported general or vision-related quality of life

None of the included trials measured or reported this outcome.

#### Change in visual function

None of the included trials measured or reported this outcome.

#### Change in tear film break-up time

Twelve trials reported on changes in tear break-up time (TBUT). Ten trials measured changes in TBUT with fluorescein dye instilled (Aragona 2013; Byun 2012; Chen 2020; Lee 2014; Lin 2015; Luo 2013; Pinto-Fraga 2016; Qazi 2015; Singla 2019; Wan 2012). In two trials, the investigators applied a novel, non-invasive technique for measuring TBUT (non-invasive keratograph break-up time [NIKBUT]) alone ( Cao 2018) or along with the routine fluorescein dye instillation (Li 2021).

### *Important outcomes*

#### Change in ocular surface staining

Twenty trials reported on changes in corneal staining, and eight trials reported on changes in conjunctival staining. We chose to report corneal staining data to assess corticosteroid effects on changes in ocular surface staining. Eleven of the 20 trials that implemented corneal staining exam followed the National Eye Institute (NEI) scoring scheme (Akhlaq 2019; Aragona 2013; Avunduk 2003; Bausch 2013; Byun 2012; KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); Sheppard 2014; Singla 2019), and reported an overall score ranging from 0 to 15 (Lemp 1995). Lin 2015 used a modified scoring system based on a previously published grading system (Macri 2000; Qiu 2011).

Pinto-Fraga 2016 applied two scoring schemes to grade the corneal staining image (Bron 2003; Jones 2002); we chose to extract and include staining scores based on the Oxford system (Jones 2002).

#### Change in tear osmolarity

Only two trials reported on tear osmolarity (Bausch 2013; Pinto-Fraga 2016). Bausch 2013 reported on changes in tear osmolarity of the worse eye between baseline and 12 weeks of intervention. Pinto-Fraga 2016 reported on changes in tear osmolarity from baseline to 21 days after treatment with FML 0.1% or the vehicle, right before participants were to be exposed to adverse controlled environment (Pinto-Fraga 2016).

#### Change in aqueous tear production

Nine trials used the Schirmer's test, without anesthesia (Byun 2012; Chen 2020; Li 2021; Lin 2015; Luo 2013; Pinto-Fraga 2016; Sheppard 2014; Singla 2019; Wan 2012), while one trial used it with anesthesia (Qazi 2015). One trial did not report numeric results, only stating that "no significant change in the mean Schirmer test score was observed in either group" (Lin 2015).

#### Adverse effects

We prespecified four adverse effects of interest: ocular complications, elevated IOP, new cataract formation, and delayed or impaired wound healing (Liu 2021). Five trials reported on 'any' systemic or ocular adverse events, as well as specific ocular adverse

events, such as elevated IOP (KPI-121 (Phase 2); KPI-121 (STRIDE1); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223). Six other trials reported specifically on IOP elevation, Bausch 2013; Byun 2012; Lin 2015; Pflugfelder 2004; Sheppard 2014, or new cataracts (KPI-121 (STRIDE3); Pflugfelder 2004). Only two trials reported on delayed or impaired wound healing (Pinto-Fraga 2016; Sheppard 2014).

### Excluded studies

After screening 54 full-text reports or trial registry records, we excluded 21 studies, with reasons for their exclusion provided in Characteristics of excluded studies. Among these 21 studies, 16 had an ineligible study design; two enrolled ineligible patient populations; two examined ineligible interventions; and one was terminated before participant recruitment.

### Ongoing studies and studies awaiting classification

Four trials, registered between February 2020 and May 2021 on trial registries (CTRI/2021/02/031182; ISRCTN16288419; NCT04734197; NCT04734210), are still recruiting participants. We assessed a further six trials as awaiting classification because, to our knowledge, no published results are available despite their being completed (ChiCTR-IPR-15007196; NCT00471419; NCT00560638; NCT01562795; NCT03418727; NTR2291). We contacted these trial investigators (or the sponsoring companies) at least twice, but have not received any response. We also assessed Herman 2005 as awaiting classification because the findings were available only in a conference abstract, with no details about the sample size of the comparison group; the first author has not yet responded to our inquiries.

## Risk of bias in included studies

We applied the RoB 2 tool to assess two critical outcomes: patient-reported symptoms (Figure 2) and corneal fluorescein staining (Figure 3). Twenty-one trials (95% of the 22 included trials) reported either outcome. Domain-specific judgements and the supporting statements for each study are provided in Characteristics of included studies. For both outcomes, we judged two trials to be at low risk of bias across all the domains assessed (KPI-121 (Phase 2); KPI-121 (STRIDE1)); we also judged a third trial to have a low risk of bias for the objective outcome, but not for patient-reported symptoms, due to concerns regarding selective reporting of trial results (KPI-121 (STRIDE2)). We judged the other trials as having some concerns or high risk of bias.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias domain for each included trial that reported patient-reported symptom scores.**

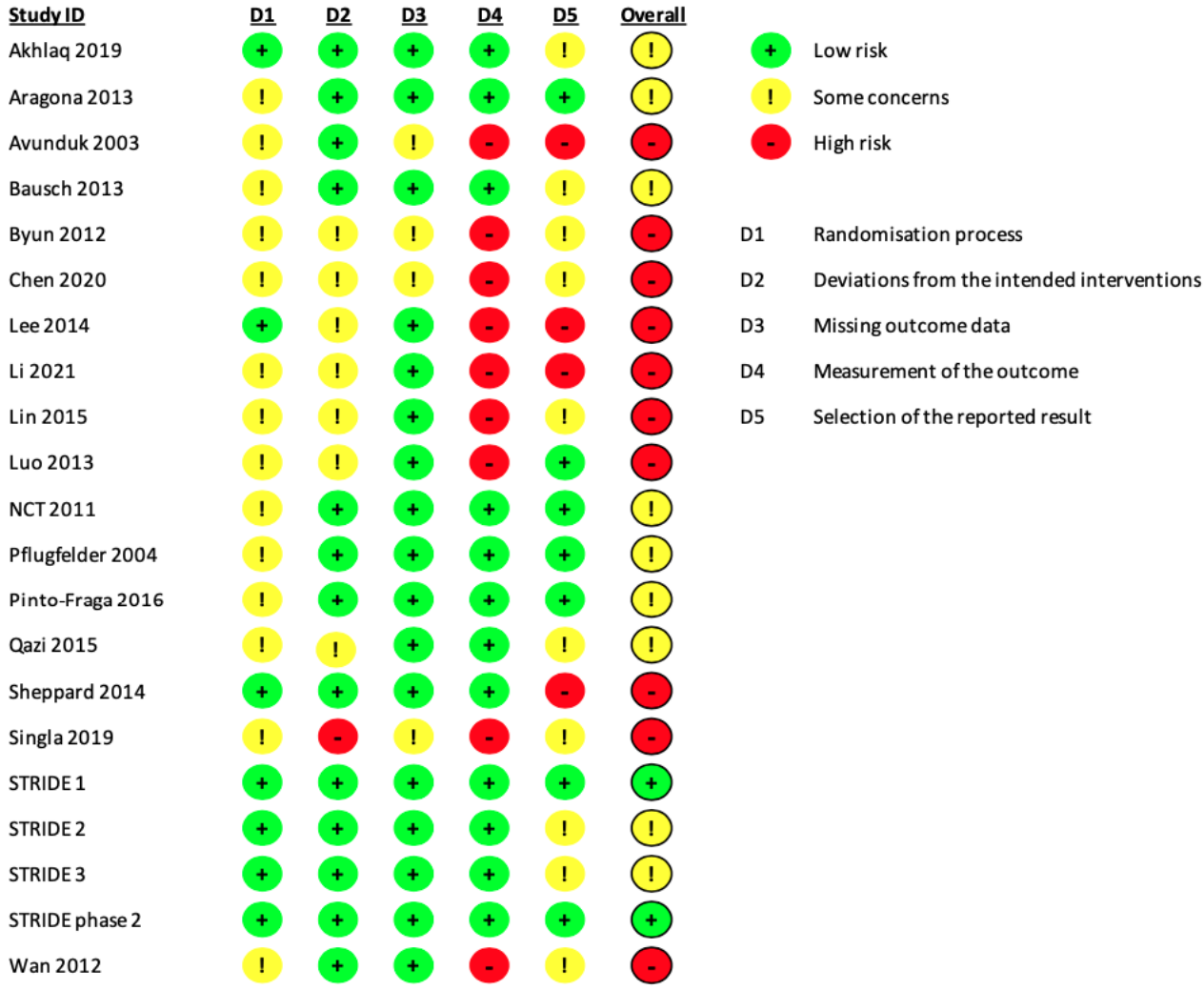
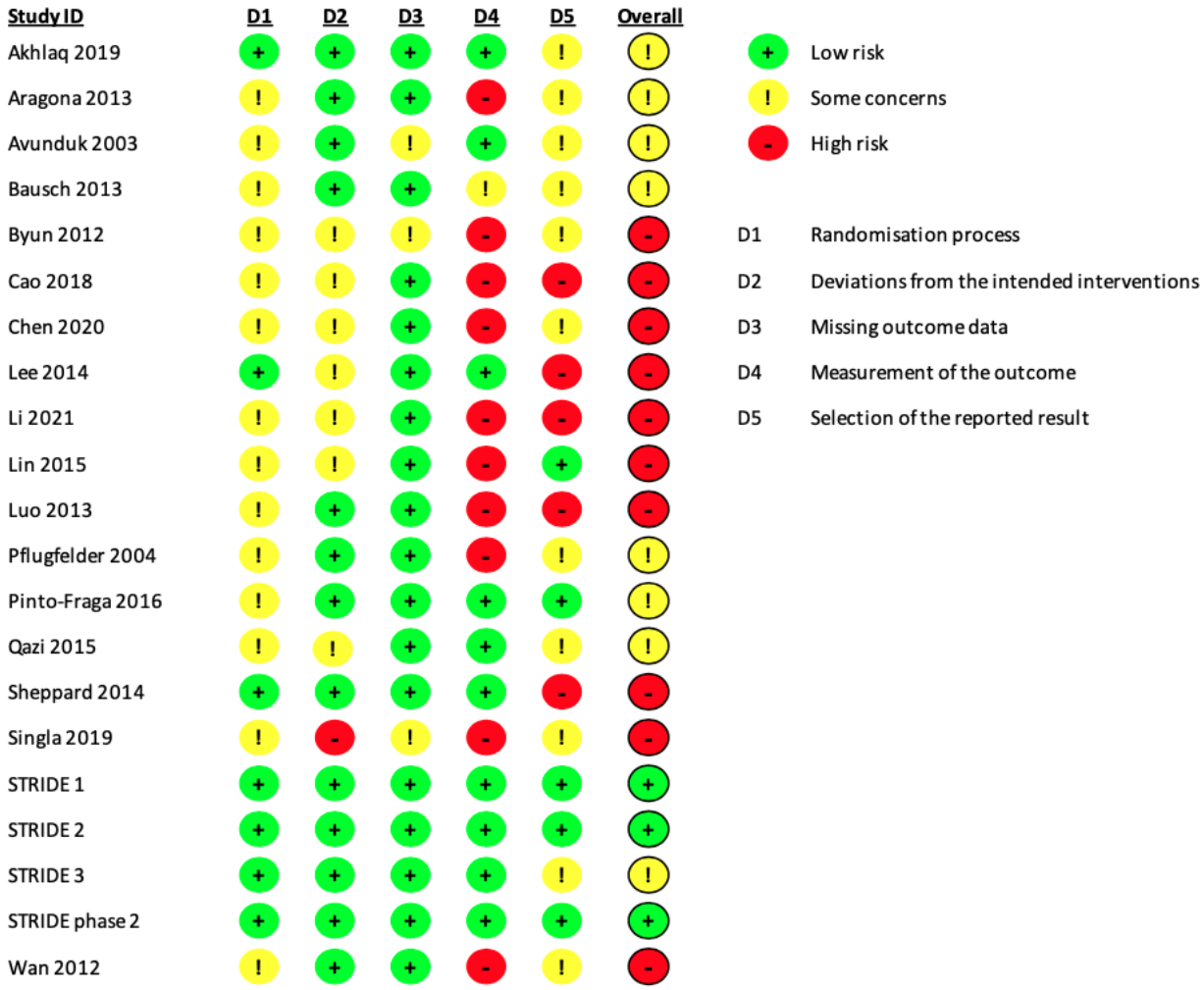


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias domain for each included trial reporting corneal fluorescein staining results.**




**Domain 1: Bias arising from the randomization process**

***Change in patient-reported symptom scores, change in corneal fluorescein staining scores***

For both outcomes, seven of the 21 trials adequately described the process of random number generation and whether the allocation was concealed before assigning participants (33%), and were thus considered to be at low risk of bias. In the other 14 trials (67%), study authors simply mentioned randomization, but did not provide sufficient details to permit a risk of bias assessment, therefore we categorized these trials as having some concerns for this domain.

**Domain 2: Bias arising from deviations from intended interventions**

***Change in patient-reported symptom scores, change in corneal fluorescein staining scores***

We judged Singla 2019 to have high risk of bias because it was unclear whether the authors applied intention-to-treat analysis to estimate the effect of assignment. Six trials did not report whether trial participants or assessors were masked, therefore we had some concerns about potential biases associated with deviating from the intended interventions. We also had some concerns in one of the three-arm trials, Qazi 2015, regarding how participants were masked because of inconsistent reporting in the trial report and on ClinicalTrials.gov. We assessed the remaining 13 trials (62%) and 12 trials (57%) as at low risk of bias for patient-reported symptom scores and change in corneal fluorescein staining scores, respectively.

**Domain 3: Bias due to missing outcome data**

***Change in patient-reported symptom scores, change in corneal fluorescein staining scores***

In 18 of the 21 trials (86%) that reported symptoms or corneal staining scores, study authors reported data for both outcomes for all or nearly all participants initially randomized to the intervention and comparator treatments. For example, Sheppard and colleagues initially randomized 116 participants into two comparison groups and reported data for both outcomes in 112 individuals (Sheppard 2014). The authors did not specify the

numbers of participants randomized or lost to follow-up in each group, but we judged that the bias associated with missing data would be minimal, and therefore assessed the study as at low risk of bias, similar to the other 17 trials.

In contrast, we assessed two trials with small or moderate sample sizes as having some concerns associated with missing outcome data, because the authors reported that four participants in total were withdrawn from the study (Avunduk 2003, N = 19), or an unknown number of participants who did not complete the study visits were excluded from data analysis (Singla 2019). We also judged one additional trial to have some concerns for this domain because of inconsistent reporting between the full-text publication and the conference abstract (Byun 2012).

**Domain 4: Bias in outcome measurement**

***Change in patient-reported symptom scores***

We judged nine trials (43%) that were open-label (Lin 2015), unmasked to participants (Avunduk 2003; Lee 2014), or unclear about the masking status of participants (Byun 2012; Chen 2020; Li 2021; Luo 2013; Singla 2019; Wan 2012), as at high risk of bias in measuring this outcome. In comparison, we considered the other 13 trials as at low risk of bias because participants were masked to the treatment received.

***Change in corneal fluorescein staining scores***

The experience of clinical authors of this review suggests that grading of the corneal staining images could be subjective and might be influenced by the knowledge of the intervention. As such, we judged one open-label trial, Lin 2015, and nine trials that did not provide masking information about the examiners or assessors who performed or graded the corneal staining images, Aragona 2013; Byun 2012; Cao 2018; Chen 2020; Li 2021; Luo 2013; Pflugfelder 2004; Singla 2019; Wan 2012, as having high risk of bias in measuring or assessing this outcome. Although there was no statistical evidence that the outcome assessment was differentially influenced by the open-label design in Bausch 2013, we still considered this study as having some concerns related to risk of bias in measuring this outcome. We judged the other six trials as at low risk of bias for this domain.

**Domain 5: Bias in selective reporting of outcome data**

***Change in patient-reported symptom scores***

In seven trials, the investigators analyzed and reported this outcome as prespecified in the study protocol or as one of the outcome variables considered in sample size calculations (Aragona 2013; KPI-121 (STRIDE1); NCT01276223; Pflugfelder 2004; Pinto-Fraga 2016), or in a standard manner as described in the methods section (KPI-121 (Phase 2); Luo 2013); we judged these trials as at low risk of bias for selective outcome reporting.

We considered five trials as having some concerns due to inconsistent reporting of outcome metrics with what was specified in the study protocol, the analytic plan, or the trial registry records (Akhlaq 2019; KPI-121 (STRIDE2); KPI-121 (STRIDE3); Lin 2015; Qazi 2015). We had some concerns with another five trials because no prespecified analytic plans were available for assessment (Bausch 2013; Byun 2012; Chen 2020; Singla 2019; Wan 2012).

We judged four trials as at high risk of bias due to apparent deviations from the analytic plan (Avunduk 2003; Lee 2014; Li 2021; Sheppard 2014).

***Change in corneal fluorescein staining scores***

Two trials reported this outcome as planned and were thus judged to be at low risk of bias for this domain (Lin 2015; Pinto-Fraga 2016). We judged two trials as having some concerns related to risk bias because of incomplete reporting (Avunduk 2003; Pflugfelder 2004), along with another six trials that did not provide access to protocols for evaluation (Akhlaq 2019; Aragona 2013; Bausch 2013; Byun 2012; Chen 2020; Qazi 2015).

We considered three trials as at high risk of bias because of deviations from their planned analysis (Lee 2014; Li 2021; Sheppard 2014). We also considered Cao 2018 and Luo 2013 to have high risk of bias for selective outcome reporting because of incomplete reporting.

**Overall assessment of bias**

***Change in patient-reported symptom scores***

For this subjective outcome, we judged 10 trials (48%) as at high risk of bias, mostly because of potential risks associated with biased measurement or selective reporting (Figure 2). We considered another nine trials (43%) to have some concerns associated with the process of allocation concealment or selective outcome reporting. Overall, selective outcome reporting was a major source of bias for trials that had reported this subjective outcome.

***Change in corneal fluorescein staining scores***

For this outcome, we judged 10 trials (48%) as having a high risk of bias, potentially due to biased measurement or selective reporting of results (Figure 3). Singla 2019 was the only trial that we judged to be at high risk of potential deviations from the intended intervention. We deemed another eight trials (38%) as having some concerns in the randomization process or outcome reporting. In summary, corneal staining scores reported by the included trials also shared a similar risk of bias profile to that of the subjective outcome, with selective outcome reporting being the most common source of potential bias.

## Effects of interventions

See: **Summary of findings 1** Steroids compared with lubricants; **Summary of findings 2** Steroids compared with cyclosporine A

Sixteen of the 22 included trials (73%) evaluated the effectiveness and safety of topical corticosteroid, alone or in combination therapy, with a lubricant-like control treatment, such as AT, HA, vehicle, or no treatment (Summary of findings 1). We also included Luo 2013, which compared DEXA plus tobramycin with AT plus tobramycin, in Comparison 1. In Comparison 2, we included six trials that compared corticosteroid with CsA (Summary of findings 2).

**Comparison 1: topical corticosteroids versus lubricants**

***Critical outcomes***

**Change in patient-reported symptom scores**

A total of 15 trials comparing topical corticosteroid alone or in combination with tobramycin measured patient-reported

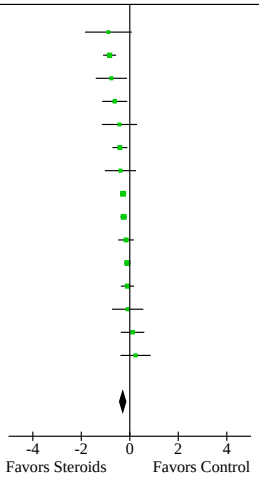
symptoms (Analysis 1.1). One three-arm study contributed data of two interventions, LE 0.5% alone and LE 0.5% plus tobramycin, separately, to this comparison (Qazi 2015).

When including LE data from the three-arm trial, Qazi 2015, topical corticosteroids alone or with tobramycin probably improve patient-reported symptom by reducing 0.29 standardized mean difference (SMD) (95% confidence interval [CI] 0.16 to 0.42 ; n = 3654) relative to lubricants ($I^2$ = 62%, P < 0.001) (Figure 4). Based on estimates obtained from the subgroup that applied the OSDI scale (9 trials, n = 3122), steroids may reduce 4.0 out of 100 points (95% CI 1.6 to 6.4) on the OSDI scale when compared with lubricants (Analysis 1.2). Results were similar when the analysis included the LE + tobramycin data from Qazi 2015 (Analysis 1.3; Analysis 1.4) or excluded a trial that had reported at eye level (Li 2021). A planned subgroup analysis by etiology found no statistical support for differential impacts of steroids on symptoms in study participants with Sjögren syndrome, MGD, or mixed etiologies (P = 0.32) (Analysis 1.5; Figure 5).

**Figure 4. Forest plot of comparison 1: Steroids versus lubricants, outcome: 1.1 Patient-reported symptom scores. The analysis included data of the LE group in Qazi 2015.**

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|---|---|
| Avunduk 2003 (1) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.6% | -0.88 [-1.85 , 0.08] | ? + ? - - - |
| Li 2021 (2) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.2% | -0.83 [-1.10 , -0.56] | ? ? + ? - - |
| Aragona 2013 (3) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.2% | -0.76 [-1.40 , -0.12] | ? + + + + ? |
| Lee 2014 (4) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.5% | -0.62 [-1.14 , -0.10] | + ? + - - - |
| Luo 2013 (5) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] | ? ? + - + - |
| Chen 2020 (6) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] | ? ? ? - ? - |
| Akhlaq 2019 (7) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.2% | -0.38 [-1.03 , 0.26] | + + + + ? ? |
| KPI-121 (STRIDE1) (8) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 13.0% | -0.28 [-0.41 , -0.15] | + + + + + + |
| KPI-121 (STRIDE3) (8) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.9% | -0.25 [-0.38 , -0.12] | + + + + ? ? |
| KPI-121 (Phase 2) (9) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] | + + + + + + |
| KPI-121 (STRIDE2) (8) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.9% | -0.10 [-0.23 , 0.03] | + + + + ? ? |
| NCT01276223 (10) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] | ? + + + + ? |
| Qazi 2015 (11) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] | ? ? + + ? ? |
| Pflugfelder 2004 (12) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] | ? + + + + ? |
| Pinto-Fraga 2016 (13) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] | ? + + + + ? |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.29 [-0.42 , -0.16]** | |

Heterogeneity: Tau² = 0.03; Chi² = 36.86, df = 14 (P = 0.0008); I² = 62%
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable



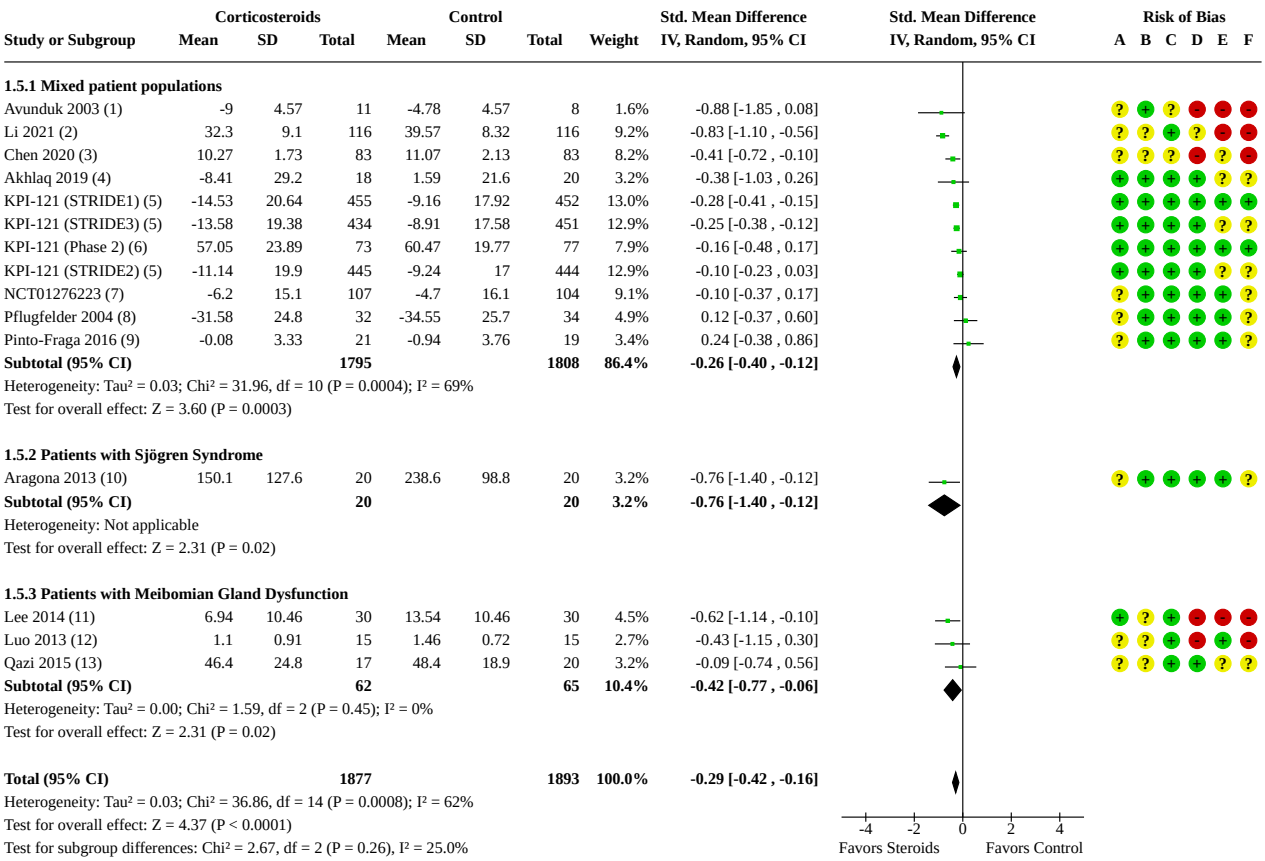

**Footnotes**

(1) At day 30, dry eye screening questionnaire for DEEP; FML (conc. unknown)
(2) At week 4, FML 0.1%; unit of analysis was eye
(3) At day 30, VAS; CB 0.1%
(4) At month 2, LE 0.5%
(5) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(6) At month 1, LE 0.1%
(7) At week 6, OSDI; LE 0.5%
(8) At day 14, OSDI; LE 0.25%
(9) At day 28, OSDI; LE 0.25%
(10) At week 4, VAS; difluprednate 0.05%
(11) At week 4, OSDI; LE 0.5%
(12) At week 4, VAS; LE 0.5%
(13) At day 21, OSDI; FML 0.1%

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

**Figure 5. Forest plot of comparison 1: Steroids versus lubricants, outcome: 1.5 Patient-reported symptom scores, with subgroup analysis by etiology of dry eye. The analysis included data of the LE group in Qazi 2015.**




**Footnotes**

(1) At day 30, dry eye screening questionnaire for DEEP; FML (conc. unknown)
(2) At week 4, FML 0.1%; unit of analysis was eye
(3) At month 1, LE 0.1%
(4) At week 6, OSDI; LE 0.5%
(5) At day 14, OSDI; LE 0.25%
(6) At day 28, OSDI; LE 0.25%
(7) At week 4, VAS; difluprednate 0.05%
(8) At week 4, VAS; LE 0.5%
(9) At day 21, OSDI; FML 0.1%
(10) At day 30, VAS; CB 0.1%
(11) At month 2, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(13) At week 4, OSDI; LE 0.5%

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

In contrast, we identified substantial subgroup differences in the estimated steroid effects by quality of the trials (P < 0.001, $I^2$ = 93.6%) (Analysis 1.6) and source of trial sponsorship (P < 0.001, $I^2$ = 89.8%) (Analysis 1.7). The combined effect of corticosteroids on symptoms was reduced by 34% when excluding trials that were judged to be at high risk of bias (SMD −0.17, 95% CI −0.27 to −0.07; 10 trials, n = 3243) (Analysis 1.6). Trial quality and source of funding were closely related with each other (Analysis 1.7). Additional analysis by steroid structure (Analysis 1.8) or treatment duration (Analysis 1.9) found no evidence for subgroup differences.

We judged the certainty of the evidence for this outcome to be moderate, downgrading for associated risk of bias in outcome measurement and selective reporting (−1).

**Change in patient-reported quality of life scores**

None of the included trials measured this outcome.

#### Change in visual function

None of the included trials measured this outcome.

#### Change in tear film break-up time

Investigators of seven trials measured TBUT using the conventional invasive technique (Aragona 2013; Cao 2018; Chen 2020; Lee 2014; Li 2021; Pinto-Fraga 2016; Qazi 2015). The combined estimate from 587 participants suggested that steroids may slightly increase TBUT by 0.70 seconds (95% CI 0.06 to 1.34) as compared with lubricants ($I^2$ = 79%, P < 0.001) (Analysis 1.10).

Estimates were similar when including the LE + tobramycin data of Qazi 2015 or the NIKBUT data reported by Li 2021 (Analysis 1.11). Post hoc subgroup analysis by structure of steroids suggested no differential effects by structural variants of topical steroids (P = 0.94, $I^2$ = 0%) (Analysis 1.12).

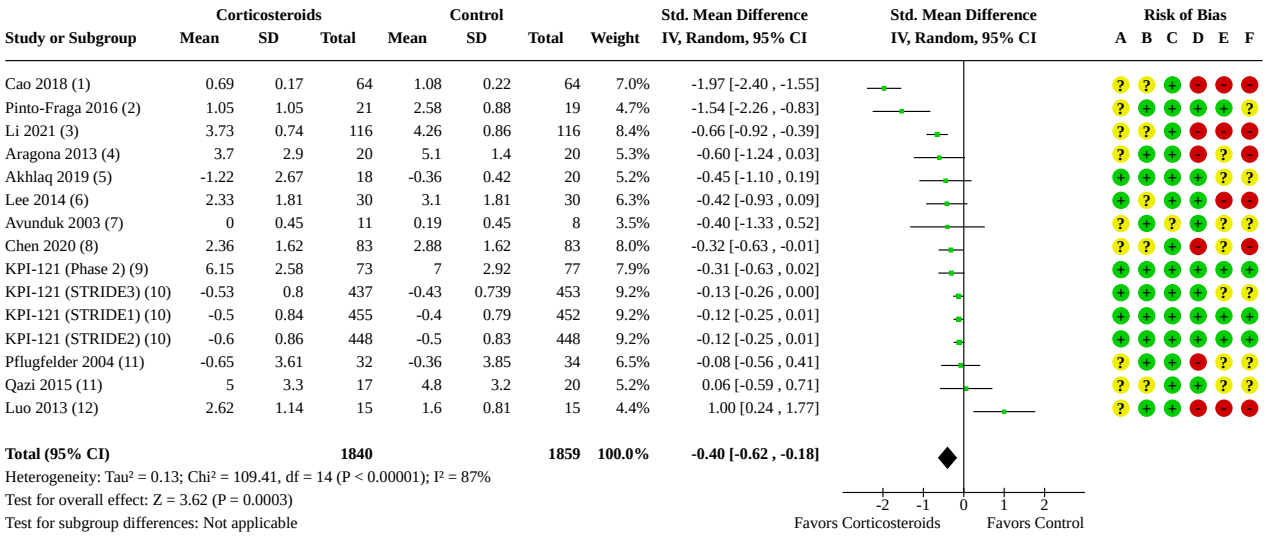
We consider the certainty of the evidence as low for this outcome because of potential risk of bias in the randomization process (−1) and unexplained heterogeneity (−1).

### *Important outcomes*

#### Change in fluorescein corneal staining scores

Of the 16 trials comparing corticosteroid, alone or with tobramycin, with lubricants, 15 trials measured corneal staining scores at one or more postintervention visits (Analysis 1.13). Based on data from 3583 participants, topical steroids probably improve corneal staining scores by 0.40 SMD (95% CI 0.18 to 0.62 ) as compared with lubricants ($I^2$ = 87%, P < 0.001) (Figure 6). The estimated effect was reduced by 70% in a subgroup of trials that used the NEI grading scheme (mean difference [MD] −0.12, 95% CI −0.19 to −0.04) (Analysis 1.14).

**Figure 6. Forest plot of comparison 1: Steroids versus lubricants, outcome: 1.13 Corneal fluorescein staining scores. The analysis included data of the LE group in Qazi 2015.**




**Footnotes**

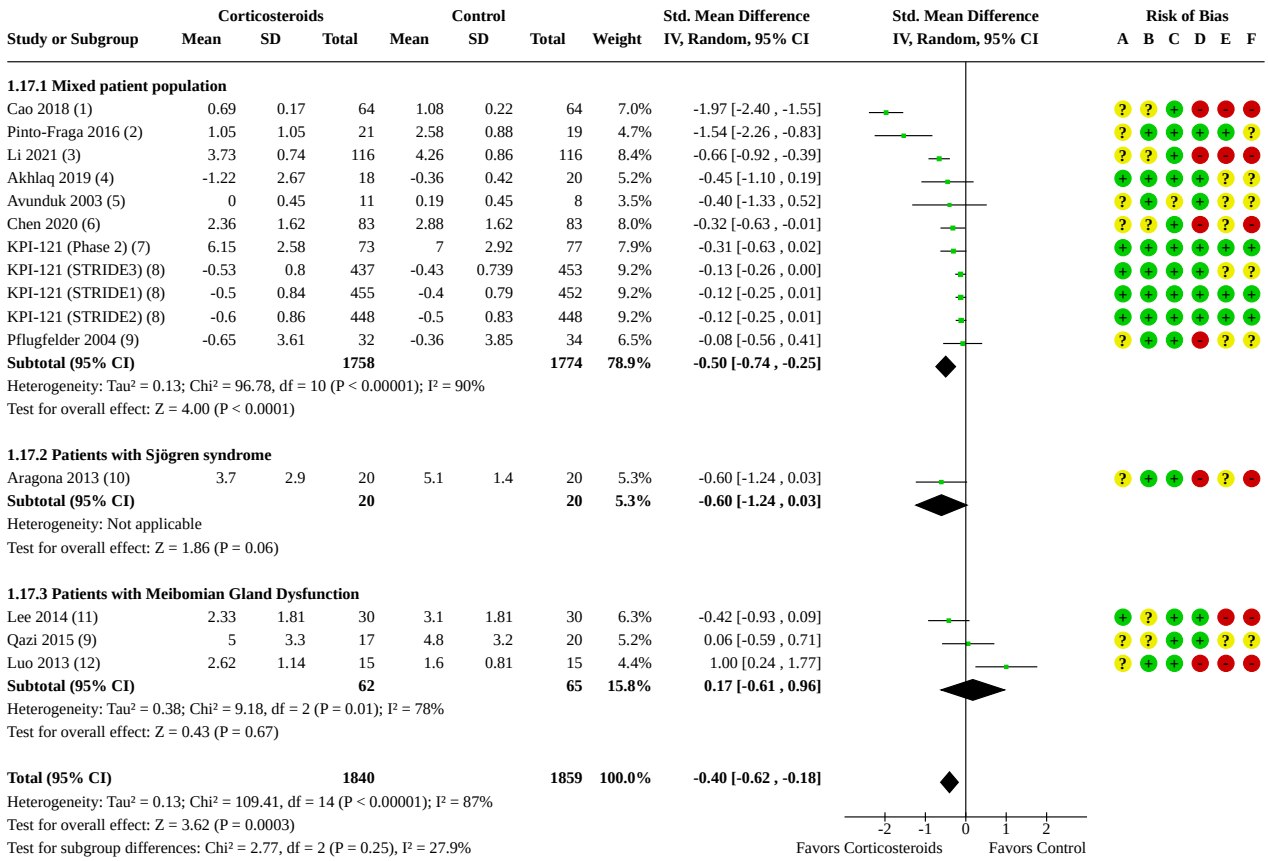
(1) At week 6, LE (conc. unknown)
(2) At day 21, FML 01%, Oxford grading scheme and Waterloo grading system
(3) At week 4, FML 0.1%; unit of analysis was eye
(4) At day 30, CB 0.1%, NEI grading
(5) At week 6, LE 0.5%, NEI grading
(6) At month 2, LE
(7) At day 30, FML, NEI grading
(8) At month 1, LE 0.1%
(9) At day 28, LE 0.25%, NEI grading
(10) At day 14, LE 0.25%, NEI grading change scores
(11) At week 4, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin, grading according to Macri and Qiu

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Including the combined intervention data of Qazi 2015 (Analysis 1.15; Analysis 1.16), or excluding eye-level data (Li 2021), did not alter the results. There were no significant subgroup differences in subgroup analysis by etiology (Figure 7), risk of bias assessment results (Analysis 1.18), source of sponsorship (Analysis 1.19), or treatment duration (Analysis 1.20).

**Figure 7. Forest plot of comparison 1: Steroids versus lubricants, outcome: 1.17 Corneal fluorescein staining scores, with subgroup analysis by etiology of dry eye. The analysis included data of the LE group in Qazi 2015.**




**Footnotes**

(1) At week 6, LE (conc. unknown)
(2) At day 21, FML 01%, Oxford grading scheme and Waterloo grading system
(3) At week 4, FML 0.1%, unit of analysis was eye
(4) At week 6, LE 0.5%, NEI grading
(5) At day 30, FML, NEI grading
(6) At month 1, LE 0.1%
(7) At day 28, LE 0.25%, NEI grading
(8) At day 14, LE 0.25%, NEI grading change scores
(9) At week 4, LE 0.5%
(10) At day 30, CB 0.1%, NEI grading
(11) At month 2, LE
(12) At week 1, dexamethasone + tobramycin vs. ATS + tobramycin, grading according to Macri and Qiu

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Overall, we judged the certainty of the evidence for this outcome as moderate after considering the associated risk of bias in outcome measurement and selective reporting (−1).

### Change in tear osmolarity

Pinto-Fraga 2016 was the only trial to report this outcome. The single study estimate suggested that corticosteroids may decrease or increase tear osmolarity (MD 1.60, 95% CI −10.47 to 13.67 mOsm/kg) after 21-day treatment but before the study participants (n = 40) were exposed to adverse controlled environment (ACE) exposure (Analysis 1.21). The certainty of the evidence for this outcome estimate was very low because of risk of bias (−2) and imprecision (−1).

#### Change in Schirmer's test scores

Only five of the 16 trials reported results of Schirmer's test, with or without anesthesia, before and after 21 to 30 days of corticosteroid treatment (Analysis 1.22). Based on the combined estimate, the evidence was very uncertain regarding the effect of steroids on Schirmer's test results (MD 0.94 mm, 95% CI 0.39 to 1.49) when compared with lubricants (n = 425; $I^2$ = 41%, P = 0.15). However, sensitivity analysis that included the LE + tobramycin data of Qazi 2015 showed that topical steroids might have little or no effect on tear production (MD 0.69, 95% CI −0.02 to 1.39). Whether LE exerted a greater effect on improving Schirmer's test than FML when compared with lubricants also varied by which intervention data (LE versus LE + tobramycin) of Qazi 2015 were being considered (Analysis 1.24). As such, we judged the certainty of the evidence for this outcome to be very low because of inconsistency (−1), risk of bias associated with the randomization process (−1), and imprecision due to the small sample size of this one trial (−1).

### *Adverse effects*

#### Proportion of participants with elevated IOP

Combining data reported by eight of the 16 trials on the occurrence of elevated IOP, the estimate suggested that steroids may increase the risk of elevated IOP by nearly five-fold when compared with lubricants (risk ratio [RR] 5.96, 95% CI 1.30 to 27.38; n = 2264); however, the evidence was very uncertain. Results of subgroup analysis by steroid structure did not support differential risks by steroid type (P = 0.31, $I^2$ = 3.1%) (Analysis 1.26). Because of varied definitions for IOP elevation across the included trials and non-reporting of this important adverse effect, we considered the certainty of the evidence as very low due to high risk of bias associated with biased measurement and selective reporting (−2) as well as imprecision (−1).

#### Proportion of participants with new cataract formation

The majority of the included trials did not measure or report incidents of cataract formation. Only one of the three trials that monitored the occurrence of cataract formation documented one incident case at the end of the 14-day trial period (Analysis 1.27). The single study estimated RR was 0.34 (95% CI 0.01 to 8.22; n = 1205), suggesting that the evidence was very uncertain for the effect of topical steroids on cataract formation. Besides imprecision (−1), concerns about undersurveillance and selective outcome reporting (−2) led to a judgement of the certainty of the evidence for this outcome as very low.

#### Proportion of participants with any ocular complication

Thirteen trials (81%) reported proportions of participants with any systemic or ocular adverse events during the study period, but none of these trials provided separate estimates for systemic and ocular incidents. Investigators in four of the 13 trials stated that they had not noticed any complaints from the study participants during a trial period lasting between 21 day and 2 months (Aragona 2013; Avunduk 2003; Lee 2014; Pinto-Fraga 2016). Based on published results on ClinicalTrials.gov (KPI-121 (Phase 2); KPI-121 (STRIDE2); KPI-121 (STRIDE3); NCT01276223), the combined estimated RR was 3.03 (95% CI 0.82 to 11.13; n = 2167; $I^2$ = 0%), suggesting that the evidence was very uncertain for differences in risk of serious adverse effects, either systemic or ocular, when comparing topical steroids with lubricants (Analysis 1.28). Overall, we judged the certainty of the evidence to be very low because of risk of bias associated with under-reporting or selective reporting (−2) and imprecision (−1).

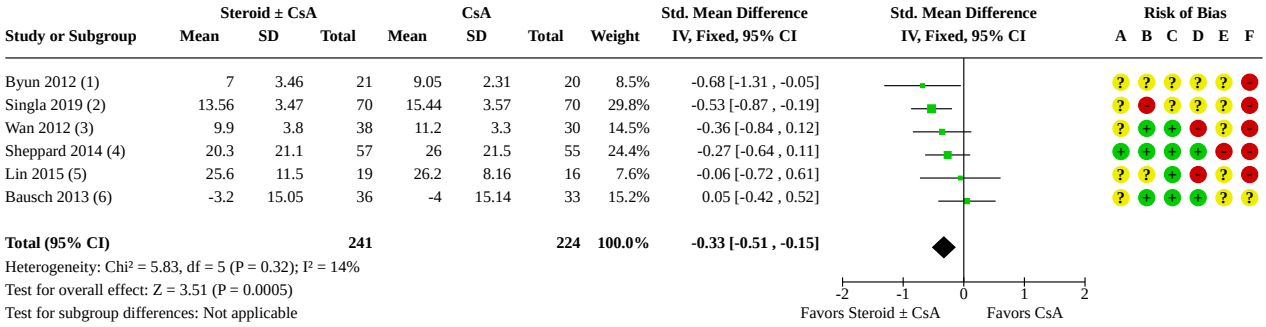
## Comparison 2: topical corticosteroid versus cyclosporine A

### *Critical outcomes*

#### Change in patient-reported symptom scores

All six trials comparing corticosteroid with CsA reported this outcome (Analysis 2.1). One three-arm trial, Bausch 2013, contributed data to two intervention groups, one with LE gel 0.5% alone and the other with LE gel 0.5% and topical CsA. The combined estimate suggested that corticosteroids, alone or in combination, may slightly improve patient-reported symptoms by 0.33 SMD (95% CI 0.15 to 0.51) as compared with CsA alone ($I^2$ = 14%; n = 465) (Figure 8). Results were similar when considering the combined intervention from Bausch 2013 (Analysis 2.2).

**Figure 8. Forest plot of comparison 2: Steroids versus cyclosporine A, outcome: 2.1 Patient-reported symptom scores. The analysis included data of the LE group in Bausch 2013.**




**Footnotes**

(1) At month 3, MP 1% + CsA
(2) At month 3, OSDI; LE 0.5% + CsA
(3) At week 8, LE 0.5% alone
(4) At day 60, OSDI; LE 0.5% four times per day for 2 weeks, concurrent LE + CsA twice per day for the rest of the study
(5) At week 8, OSDI; FML 0.1% alone
(6) At week 12, OSDI; LE gel 0.5% alone

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

The small number of trials precluded the performance of planned subgroup analysis by etiology. We did not perform a sensitivity analysis that excluded trials at high risk of bias or those sponsored by industry for the same reason. Exploratory subgroup analysis by intervention regimen (Analysis 2.3) or duration of steroid treatment (Analysis 2.4) did not find significant subgroup differences. We considered the certainty of the evidence to be low, downgrading for risk of bias (−1) and imprecision (−1).

#### Change in patient-reported quality of life scores

None of the included trials measured this outcome.

#### Change in visual function

None of the included trials measured this outcome.

#### Change in tear film break-up time

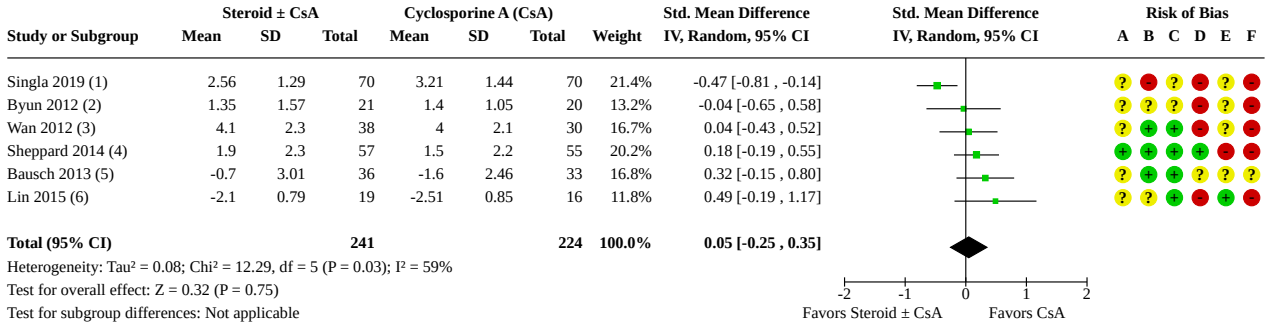
Five trials reported this outcome, evaluating the effects of corticosteroid alone, Bausch 2013; Lin 2015; Wan 2012, or in combination with CsA, Bausch 2013; Byun 2012; Singla 2019, compared with CsA (Analysis 2.5). Using data from 353 participants, the combined estimate for differences in TBUT was 0.37 seconds longer (95% CI 0.13 shorter to 0.87 longer) in the steroid group than in the CsA group, suggesting little to no difference in TBUT ($I^2$ = 72%, P = 0.007). Considering data for the combined intervention group from Bausch 2013 did not alter the conclusions (Analysis 2.6). Exploratory subgroup analysis by intervention regimen (Analysis 2.7) or duration of steroid use (Analysis 2.8) did not help in identifying sources of heterogeneity. We judged the certainty of the evidence for this outcome as low because of risk of bias (−1) and imprecision (−1).

### *Important outcomes*

#### Change in fluorescein corneal staining scores

Six trials reported corneal fluorescein staining according to the NEI grading system, Bausch 2013; Byun 2012; Sheppard 2014; Singla 2019, or an unidentified scoring system (Lin 2015; Wan 2012). The combined estimated SMD was 0.05 (95% CI −0.25 to 0.35; n = 465) (Figure 9), suggesting that corticosteroids, alone or with CsA, may not reduce corneal staining scores when compared with CsA alone (Analysis 2.9). The result was similar when including data for the combined intervention group from Bausch 2013 (Analysis 2.10).

**Figure 9. Forest plot of comparison 2: Steroids versus cyclosporine A, outcome: 2.9 Corneal fluorescein staining scores. The analysis included data of the LE group in Bausch 2013.**




**Footnotes**

(1) At month 3, LE 0.5% + CsA; NEI grading
(2) At month 3, MP 1% + CsA; NEI grading
(3) At week 8, LE 0.5% alone
(4) At day 60 (OD), LE 0.5% + CsA; NEI grading
(5) At week 12, LE gel 0.5% alone; NEI grading
(6) At week 8, FML 0.1% alone

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Post hoc subgroup analysis by grading system (Analysis 2.11), intervention regimen (Analysis 2.12), or duration of steroid treatment (Analysis 2.13) did not identify any potential sources of between-study heterogeneity. We judged the certainty of the evidence as low because of associated risk of bias (−1) and imprecision (−1).

#### Change in tear osmolarity

Bausch 2013 was the only trial to document changes in tear osmolarity (mOsm/kg) before and after the intervention with LE gel 0.5% alone or LE gel 0.5% plus CsA (Analysis 2.14).In comparison with tear samples from participants receiving CsA alone, tear samples collected from participants had a 5.80 mOsm/kg (95% CI −0.94 to 12.54) or 2.20 mOsm/kg (95% CI −6.00 to 10.4) higher osmolarity than those receiving CsA alone, suggesting LE alone or LE + CsA may decrease or increase tear osmolarity. We judged the certainty of the evidence as very low due to imprecision (−1) and risk of bias in the randomization and allocation process as well as selective reporting (−2).

#### Change in Schirmer's test scores

Of the four trials that reported this outcome, Wan 2012 was the only trial comparing steroid monotherapy with CsA alone (Analysis 2.15). The overall combined estimate was 1.19 mm longer (95% CI 0.40 shorter to 2.77 longer; n = 361) in Schirmer's test strip in the intervention group than in the control group, suggesting little to no effects of steroids on tear production when compared with CsA alone.

In our exploration of potential sources of between-study heterogeneity, we noted that excluding Singla 2019 alone could reduce the $I^2$ statistics from 90% (P < 0.001) to 0%. Differences in the intervention regimen may also have contributed to the identified heterogeneity (Analysis 2.15). However, we found no statistical evidence for or against the use of an LE- versus MP-based regimen (Analysis 2.16). We downgraded the certainty of the evidence to very low because of risk of bias (−2) and imprecision (−1).

### *Adverse effects*

#### Proportion of participants with elevated IOP

Four trials monitored IOP elevation as adverse events during the trial period (Byun 2012; Lin 2015; Sheppard 2014; Singla 2019); three trials reported no incidents of IOP elevation, and one trial documented five incidents by the end of the 60-day intervention (Sheppard 2014). The best available estimate was 45% increased risk associated with the use of LE + CsA (RR 1.45, 95% CI 0.25 to 8.33; n = 331), suggesting that steroids may decrease or increase the risk of elevated IOP as compared with CsA alone (Analysis 2.17). We judged the certainty of the evidence to be very low, downgrading for risk of bias in outcome measurement and selective reporting (−2) and imprecision of the estimate (−1).

#### Proportion of participants with new cataract formation

None of the six trials in this comparison reported this outcome.

#### Proportion of participants with any ocular complication

Three of the six trials comparing steroids with CsA reported this outcome; two provided numeric results for three comparisons (Bausch 2013; Byun 2012), and one trial described that during the observation period, they did not notice any adverse reactions to the medications [author translation] (Wan 2012). Topical steroids, either alone (RR 0.61, 95% CI 0.11 to 3.43; 2 trials, n = 103) or in combination with CsA (RR 0.65, 95% CI 0.11 to 3.80; 2 trials, n = 110), may show no effect on risk of any ocular complication when

compared with CsA alone (Analysis 2.18). However, we judged the certainty of the evidence to be very low because of risk of bias associated with under-reporting or selective reporting (−2) and imprecision (−1).

# DISCUSSION

## Summary of main results

Based on data from 22 RCTs that compared topical corticosteroids, alone or in combination, with lubricants or CsA, topical corticosteroids probably slightly improve patient-reported symptoms when compared with lubricants (moderate certainty evidence) and may slightly improve patient-reported symptoms when compared with CsA (low certainty evidence). Topical steroids probably result in a slight reduction in corneal staining scores (moderate certainty evidence) when compared with lubricants, but may result in no difference when compared with CsA (low certainty evidence). In general, the evidence suggests that corticosteroids do not increase tear production as quantified by TBUT or Schirmer's test scores (low certainty evidence). The evidence is also very uncertain about the effect of steroids on tear osmolarity.

Topical corticosteroids may increase IOP when compared with lubricants but may not do so when compared with CsA ; the evidence for each comparison is very uncertain. Similarly, very low certainty evidence suggests that steroids may have little to no effect on cataract formation when compared with lubricants. No trials comparing corticosteroids with CsA reported cataract information as adverse events.

## Overall completeness and applicability of evidence

### Population representativeness

The study populations of the included trials were representative of the dry eye populations generally seen in the outpatient clinic. The included trials had enrolled mainly middle-aged, female participants with non-specific (or unidentified) etiologies of DED as described in the literature (Nelson 2017). Nevertheless, the small to moderate numbers of participants enrolled in most trials, and the lack of reporting of group-specific outcome data, precluded subgroup analysis by age, sex, or etiology to explore differential benefits (or harms) of topical corticosteroids as compared with lubricants or CsA.

### Pharmacologic interventions

The current review did not find evidence of reduced ocular adverse effects in participants receiving LE versus other topical steroids. Among the seven steroidal preparations listed in the protocol (Liu 2021), LE of varying concentrations was the most frequently used corticosteroid in the intervention group, particularly in industry-funded trials. As a structural variant to a typical corticosteroid such as prednisolone, LE has been described as having a low risk profile in terms of IOP elevation or cataract formation (Comstock 2018). However, we did not find statistical evidence for such differential risks of IOP elevation in a subgroup analysis by structural types of topical steroids. Insufficient numbers of included trials limited our ability to evaluate risk for cataract formation (or progression) comparing steroids with lubricants or CsA.

Given the small sample sizes and the high risk of bias in outcome measurement and reporting in trials that examined the effects of steroid in combination with CsA, we also concluded that the current evidence was insufficient in quantity and quality to suggest additional benefits of topical steroid in combination with CsA over steroid alone, when compared with CsA.

### Outcome measurement

Although the current review found statistically significant improvement in patient-reported symptoms and corneal staining scores when comparing steroids with lubricants, the clinical meaning of the effect sizes was unclear. By convention, an SMD of 0.2 is considered as a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988), suggesting that steroid effects on symptoms and corneal staining scores are probably small to moderate at most. Considering the subgroup of trials that had reported symptoms on the OSDI scale, the estimated steroid effect was also smaller than the previously published minimally important difference (MID) in OSDI scores for mild or moderate DED (4.5 to 7.3) (Miller 2010). Results of subgroup analysis that excluded trials at high risk of bias further suggested that the small to moderate effects of steroids might already be overestimated.

For the two most commonly reported review outcomes, patient-reported symptom scores and corneal fluorescein staining scores, the included trials reported the use of varied standardized or non-standardized questionnaires or grading schemes. Even within trials that had applied OSDI or the NEI scheme, the degree of between-study heterogeneity was substantial, suggesting that inconsistent application of the same scales, variations among assessors in grading or interpreting imaging results, and reporting of post-treatment endpoint scores or change scores, were all potential sources of between-study heterogeneity. As such, we advise caution in the interpretation of SMD-based findings and have provided alternative benchmarks to aid the interpretation and assessment for applicability (Summary of findings 1; Summary of findings 2).

Ocular adverse events were generally under-reported, likely due to the lack of a systematic surveillance system implemented during the trial period and the short durations of the trials. Despite being well-recognized as potential adverse effects of topical corticosteroid, elevated IOP was documented in only half of the included trials; incident cataract formation was reported by even fewer trials. As such, the small absolute risks for elevated IOP in the control groups, for instance 9 incidents per 10,000 participants using lubricants (Summary of findings 1), or 12 per 1000 participants receiving CsA (Summary of findings 2), might be underestimated. The small numbers of participants enrolled per trial and the short follow-up periods further contributed to the imprecision of both the absolute and relative risk estimates for these safety outcomes.

## Certainty of the evidence

We downgraded the certainty of the evidence for the review outcomes because of substantial risk of bias associated with: the procedure of randomly allocating treatment; biased outcome measurement due to unclear masking status of the participants or the outcome assessors; and selective results reporting. Particularly for safety outcomes, the small number of trials that had reported ocular adverse events might indicate non-reporting or

under-reporting of these events. The potential impact on the combined estimates for adverse effects of topical steroids would be underestimation of the risks of IOP elevation or cataract formation as compared with lubricants or CsA.

### Potential biases in the review process

An Information Specialist assisted with an exhaustive search in multiple electronic databases and trial registries. We applied standard Cochrane methods to conduct this review and to avoid potential biases associated with literature search, critical appraisal, data extraction, analysis, and interpretation. We also performed an additional handsearch of the references of the included trials, and made repeated efforts to contact trial investigators or study authors to clarify details regarding study design (NCT00471419), sample sizes (Herman 2005), concentrations of the intervention steroids (NCT03418727), or to request trial results (ChiCTR-IPR-15007196; NCT00560638; NCT01562795; NCT03418727; NTR2291). These efforts were not always successful, and contributed to the imprecision of the combined estimates for some comparisons.

### Agreements and disagreements with other studies or reviews

In searching for relevant reviews that had been published since 2017, we identified four review articles that examined the efficacy or effectiveness of topical corticosteroids for dry eye disease (Beckman 2020; Cutolo 2019), ocular complications of Sjögren syndrome (Shih 2017), or ocular inflammatory conditions in general (Comstock 2018); none of these were systematic reviews.

Authors of both Beckman 2020 and Cutolo 2019 included not only RCTs but also observational studies in their narrative reviews. These two reviews also included trials of paired-eye design and those that enrolled post-transplant or postcataract patients. In Beckman 2020, the authors cited study findings from two conference proceedings that were not accessible through indexed databases (Barabino 2011; Evans 2017). Findings of Beckman 2020 and Cutolo 2019 agreed with the current review in finding that topical corticosteroids were effective in improving dry eye symptoms and tear film parameters, such as TBUT and corneal staining scores, as compared with lubricants. Their conclusions were also concordant with our findings that steroid use before or concurrently with CsA was beneficial for relieving symptoms when compared with CsA alone or with artificial tears/vehicle. However, our review did not find evidence supporting the role of topical steroid in ameliorating ocular signs as stated in Beckman 2020 or Comstock 2018. Differences in eligibility criteria for study populations or study design of the original studies might have contributed to these discrepancies in findings.

In three of the four narrative reviews (Beckman 2020; Comstock 2018; Cutolo 2019), the authors also summarized evidence regarding adverse effects, concluding that topical corticosteroids, particularly LE, "provide certain safety" based on the few included trials that had reported on incident IOP elevation, though authors of Cutolo 2019 recognized that "the incidence of side effects" could vary by different (types or formulas of) topical corticosteroids. In our review, the small number of trials comparing steroid alone or in combination with CsA did not allow for reliable estimation of risks for elevated IOP. In contrast with prior qualitative reviews, our review provided quantitative evidence showing that steroid use was associated with a nearly five-fold increased risk of IOP elevation even with 'short-term' use (up to four weeks).

## AUTHORS' CONCLUSIONS

### Implications for practice

- Topical corticosteroids likely provide small to moderate improvement in symptoms as compared with artificial tears (moderate certainty evidence), and may provide small to moderate improvement in symptoms as compared with cyclosporine A (low certainty evidence).
- Evidence supports the anti-inflammatory effects of steroids on corneal staining scores over lubricants (moderate certainty evidence), but not over cyclosporine A (low certainty evidence).
- Steroids may have little to no effect on tear quality or production as shown by tear film break-up time (low certainty evidence) and Schirmer's test (low certainty evidence).
- The evidence is very uncertain regarding the effects of steroids on tear osmolarity, risk of elevated intraocular pressure, or risk of cataract formation.

### Implications for research

Whether topical corticosteroids have a role in the step-up (from lubricants or cyclosporine A) treatment strategies for dry eye patients will be better informed by future trials that:

- recruit patients of identifiable etiologies of dry eye and then report etiology-specific treatment effects;
- perform head-to-head comparisons between different types of steroids, such as ester steroids versus ketone steroids;
- measure and report quality of life or visual function-related outcomes;
- last a reasonable duration of time to allow for the detection of uncommon yet important adverse events such as intraocular pressure elevation, cataract formation or progression.

Lack of consistency in correlating signs and symptoms within the patient population of dry eye creates difficulty in determining the minimally important differences in patient-reported outcomes for different subgroups of patients. Variations in the clinical presentation of patients further emphasize the importance of unbiased measurement and reporting of these core outcomes in the same trial. Investigators should employ at least double-masking of participants and assessors (rather than examiners) to avoid potential risk of bias in documenting both subjective and objective study outcomes.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

**Akhlaq 2019**

| *Study characteristics* | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group |

**Akhlaq 2019** *(Continued)*

**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2014/02 (ClinicalTrials.gov)

**02. Calendar time when the study completed follow-up** (YYYY/MM): 2017/04 (ClinicalTrials.gov)

**03. Unit of randomization (participant or eye)**: participant (both eyes)

**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double (participant, investigator)

**05. Study visits and the corresponding time points**: baseline, 2 weeks, and 6 weeks

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI; SANDE

**07. Assessment for safety outcomes**: the occurrence of adverse events: serious vs non-serious; expected vs unexpected; changes to the use of concomitant medications; comprehensive eye examination including BCVA, measuring intraocular pressure, evaluation of the condition of conjunctiva, cornea, anterior chamber, iris/pupil, lens, vitreous, macula and optic nerve; conjunctival infections; if treatment with artificial tears is inadequate, or the participant develops a severe form of ocular surface disease and dry eye, for the safety and proper treatment of the participant, the investigator can unmask the participant's treatment assignment

**08. Planned follow-up duration**: 6 weeks

**09. Actual follow-up duration**: 6 weeks

**10. Planned treatment duration (of the intervention steroid)**: 6 weeks

**11. How missing data were handled**: the study protocol specified an ITT analysis for any withdrawal from the study

**12. Description of power and sample size calculation**: "To calculate sample size, density of sub-basal dendritic cells in the central cornea was used as an outcome measure. With $\alpha = 0.05$ ($Z\alpha = 1.96$), $d = 52$, and $p = 44$, a sample size of 22 was calculated for each group (44 for both groups). To compensate for potential loss to follow-up, a total of 50 subjects will be enrolled in this study"

| | |
|---|---|
| Participants | **Country:** USA<br><br>**Setting:** single-site, university-affiliated eye center<br><br>**Interventions**<br><br>• **Loteprednol etabonate 0.5% (Lotemax)**<br><br>Age, mean/SD (range): 57.2/12.1<br>Female, n (%): NR<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 18 (31 eyes)<br>Participants (eyes) analyzed for primary study outcomes: 18<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Soothe Emollient**<br><br>Age, mean/SD (range): 55.4/15.6<br>Female, n (%): NR<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 20 (36 eyes)<br>Participants (eyes) analyzed for primary study outcomes: 20<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Overall**<br><br>Age, mean/SD (range): 56.2/13.9<br>Female, n (%): NR |

**Akhlaq 2019** *(Continued)*

Etiology, n (%): NR
Participants (eyes) randomized: 38 (67 eyes)
Participants (eyes) analyzed for primary study outcomes: 38
Participants (eyes) analyzed for safety outcomes: NR

**Inclusion criteria**:

1. Age 18 to 89 years
2. Willing and able to provide written informed consent
3. Willing and able to comply with study assessments for the full duration of the study
4. Diagnosis of dry eye disease based on the following:
   a. symptoms of dry eye disease, such as foreign body sensation, burning, stinging, light sensitivity for at least 6 months;
   b. 2 or more of the following objective signs: Schirmer test with anesthesia < 10 mm at 5 min, TBUT of < 10 s, corneal fluorescein staining of 4 in at least 1 eye, Lissamine green staining of the nasal and temporal conjunctiva (NEI grading scheme, 0 to 18) in at least 1 eye—corneal dendritiform cell count by confocal microscopy of ≥ 75/mm$^2$ (13 immune cells per image).
5. In good stable overall health

**Exclusion criteria**:

1. Central corneal subbasal dendritic cell count by in vivo confocal microscopy of < 75/mm$^2$ in both eyes
2. Active ocular allergies
3. Active allergies to steroids, aminoglycosides, or benzalkonium chloride (BAK)
4. History of contact lens wear within 3 months before enrollment
5. Intraocular surgery or ocular laser surgery within 3 months before enrollment
6. History of ocular infection within 3 months before enrollment
7. History of topical or systemic steroid treatment within 1 month before enrollment. In case of topical steroid use, a wash-out period of 1 month is required
8. History of increased intraocular pressure after using topical steroids (steroid responsive)
9. History of systemic immunosuppressive treatment within 1 month before enrollment
10. History of any change in the frequency of topical ciclosporin or oral tetracycline compounds (tetracycline, doxycycline, and minocycline) within 1 month before enrollment
11. Any condition (including language barrier) that precludes person's ability to comply with study requirements including completion of study

**Baseline comparison**: baseline characteristics of the study population were not reported, except the baseline OSDI scores, which suggested evident differences in patient-reported symptom severity between groups (53.53 ± 29.7 vs 34.46 ± 20.33, post hoc P = 0.0255)

| | |
|---|---|
| Interventions | • **Loteprednol etabonate 0.5% (Lotemax):** 4 times a day for 2 weeks; twice daily for 2 weeks; and once daily for 2 weeks (total 6 weeks)<br>• **Soothe Emollient:** 4 times a day for 2 weeks; twice daily for 2 weeks; and once daily for 2 weeks (total 6 weeks) |
| Outcomes | **Time points of primary outcome data collected:** at 6 weeks<br><br>**Primary outcomes of the study**: IVCM for determination of:<br><br>1. density of superficial corneal epithelial cells;<br>2. size of superficial corneal epithelial cells;<br>3. hyperreflectivity of superficial corneal epithelial cells;<br>4. density of corneal immune dendritiform cells;<br>5. size of corneal immune dendritiform cells;<br>6. cell field of corneal immune dendritiform cells;<br>7. density of subbasal nerves;<br>8. number of main nerves and branches of corneal subasal nerves; |

**Akhlaq 2019** *(Continued)*

9. length of main nerves and branches of corneal subasal nerves.

**Other outcomes of the study**: corneal fluorescein staining using the NEI grading scheme; conjunctival Lissamine green staining using NEI grading scheme; TBUT, seconds; Schirmer's test with anesthesia, mm; IOP by measure of applanation tonometry, mmHg; OSDI questionnaire, total score of the OSDI questionnaire; SANDE questionnaire

| | |
|---|---|
| Study Identification | **Sponsorship source:** GlaxoSmithKline plc<br><br>**Ethics approval:** a copy of the approved protocol and study-related materials will be placed on a shared network drive accessible to authorized research staff involved in this study and on IRBnet.org<br><br>**Correspondence author's name:** Pedram Hamrah; Institution: Tufts University, Boston, MA<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT02120079 (previously NCT02106377)<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: Anam Akhlaq, none; Ahmad Kheirkhah, none; Shruti Aggarwal, none; Bernardo Cavalcanti, none; Rodrigo Mueller, none; Alessandro Abbouda, none; Zeina Salem, none; Reza Dana, Allergan (F), Claris Biotherapeutics (I), Kala (C), Santen (C), Shire (C); Pedram Hamrah, Aeri Pharmaceuticals (C), Allergan (F), Allergan (C), Axero (C), Bausch and Lomb (F), Clementia (C), Coopervision (F), Dompe (F), Dompe (C), Eyegate (C), GlaxoSmithKline (F), Heidelberg Engineering (C), Kala Pharmaceuticals (C), Novabay (C), Novaliq (C), Noveome (C), Ocunova (C), Revision Optics (C), SanoW (C), Santen (C), Shire (F), Shire (C), Tissue Tech (F), Valeant (C) |
| Notes | |

**Aragona 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): NR<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double masking<br><br>**05. Study visits and the corresponding time points**: baseline (T0), day 15 (T15), day 30 (T30), and day 45 (TFU)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: VAS (0 to 100) for each of the following symptoms: burning, itching, foreign body sensation, photophobia, sticky eye, blurred vision, and dryness. The total score was therefore obtained by adding up the results of each symptom.<br><br>**07. Assessment for safety outcomes**: IOP at each visit; fundus exam on day 30<br><br>**08. Planned follow-up duration**: 45 days<br><br>**09. Actual follow-up duration**: 45 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 30 days<br><br>**11. How missing data were handled**: NR |

**Aragona 2013** *(Continued)*

| | |
|---|---|
| | **12. Description of power and sample size calculation**: "For the study population, it was considered an assumed efficacy of the study treatment of 50% and 5% of the control treatment for an α value of 0.05, using a 2-tailed analysis, and a power of 90%, which gave a population of 38 patients in total (19 per arm) to achieve statistically significant results" |
| Participants | **Country:** Italy<br><br>**Setting:** single-site, university-affiliated eye center<br><br>**Interventions**<br><br>• **Preservative-free 2% PVP plus 0.1% CB eyedrops**<br><br>Age, mean/SD (range): 58.8/6.7<br>Female, n (%): 19 (95%)<br>Etiology, n (%): Sjögren syndrome, 20 (100%)<br>Participants (eyes) randomized: 20<br>Participants (eyes) analyzed for primary study outcomes: 20<br>Participants (eyes) analyzed for safety outcomes: 20<br><br>• **Preservative-free 2% PVP eyedrops plus a solution containing only the vehicle of the active formulation**<br><br>Age, mean/SD (range): 60.1/5.1<br>Female, n (%): 19 (95%)<br>Etiology, n (%): Sjögren syndrome, 20 (100%)<br>Participants (eyes) randomized: 20<br>Participants (eyes) analyzed for primary study outcomes: 20<br>Participants (eyes) analyzed for safety outcomes: 20<br><br>• **Overall**<br><br>Age, mean/SD (range): 59.5/5.9<br>Female, n (%): 38 (95%)<br>Etiology, n (%): Sjögren syndrome, 20 (100%)<br>Participants (eyes) randomized: 40<br>Participants (eyes) analyzed for primary study outcomes: 40<br>Participants (eyes) analyzed for safety outcomes: 40<br><br>**Inclusion criteria**:<br>One or more dry eye–related symptoms including burning, itching, foreign body sensation, photophobia, sticky eye, blurred vision, and dryness, with a VAS value above 30 mm out of 100 mm for each symptom; TBUT ≤ 3 seconds; and corneal staining with a fluorescein score ≥ 2, on a scale from 0 (absent) to 3 (severe), in at least 2 out of 5 corneal areas as described by Lemp (NEI Workshop on clinical trials in dry eyes 1995).<br><br>**Exclusion criteria**:<br>Eye injury, infections, non–dry eye ocular inflammation, or trauma or surgery within the previous 6 months; concurrent treatment able to interfere with the interpretation of the study results (systemic corticosteroids, immunosuppressive therapy, parasympathetic agents); uncontrolled disease or significant illness; or pregnancy or lactation. Postmenopausal patients on hormonal replacement therapy were also excluded.<br><br>**Baseline comparison**: no differences in age or sex distribution between groups |
| Interventions | • **Preservative-free 2% PVP plus 0.1% CB eyedrops:** CB twice a day; PVP 5 to 8 times a day (total 30 days plus 15 days of saline use)<br>• **Preservative-free 2% PVP eyedrops plus a solution containing only the vehicle of the active formulation:** vehicle twice a day; PVP 5 to 8 times a day (total 30 days plus 15 days of saline use)<br><br>PVP (Wet-Comod, Visufarma SpA, Rome, Italy); CB (Visucloben, Visufarma SpA) |
| Outcomes | **Time points of primary outcome data collected**: at day 30 |

**Aragona 2013** *(Continued)*

| | |
|---|---|
| | **Primary outcomes of the study**:<br>1. Global symptoms score<br>2. Corneal fluorescein stain score<br>3. IOP values<br>4. Epithelial cells area<br>5. HLA-DR expression on the conjunctival epithelial cells<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source:** the drugs used in the trial were provided by Visufarma SpA, Roma, Italy. The authors report no proprietary interest or financial support.<br><br>**Ethics approval:** ethical approval was granted by the Ethics Committee of the University Hospital of Messina<br><br>**Correspondence author's name:** Pasquale Aragona; Institution: Department of Surgical Specialties Section of Ophthalmology Ocular Surface Unit University Hospital of Messina, Italy<br><br>**Additional information:**<br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: the authors report no proprietary interest or financial support |
| Notes | |

**Avunduk 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): NR<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: the examiner (AMA) was masked as to the medication used by the participants. The participants were instructed to discuss their medications only with the study co-ordinator and not with the examiner.<br><br>**05. Study visits and the corresponding time points**: days 0, 15, and 30<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: "We also obtained symptom severity scores from patients who were instructed to grade their symptoms averaging the symptom severities for both eyes." The authors utilized a screening questionnaire for DEEP published by Oden NL and colleagues.<br><br>**07. Assessment for safety outcomes**: unclear—the authors did not report assessment for safety outcomes in the methods section. However, the authors mentioned in the results section that: "We did not observe any complication that could be linked to the study medications during the treatment period".<br><br>**08. Planned follow-up duration**: 30 days<br><br>**09. Actual follow-up duration**: 30 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 30 days |

**Avunduk 2003** *(Continued)*

**11. How missing data were handled**: complete-case analysis on study outcomes.

**12. Description on power and sample size calculation**: power was calculated to detect an among-group difference in change from baseline in symptom severity scores on day 30

| | |
|---|---|
| Participants | **Country**: USA<br><br>**Setting**: single-site, university-affiliated eye center<br><br>**Interventions**:<br><br>• **Topical FML drops 4 times a day plus ATS 4 to 8 times a day in both eyes for 30 days**<br><br>Age, mean/SD (range): 57.6/12.4<br>Female, n (%): 7 (64%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: NR<br>Participants (eyes) analyzed for primary study outcomes: 11<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Preservative-free topical ATS 4 times a day in both eyes for 30 days**<br><br>Age, mean/SD (range): 51.2/12.4<br>Female, n (%): 5 (63%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: NR<br>Participants (eyes) analyzed for primary study outcomes: 8<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Overall**<br><br>Age, mean/SD (range): 57.2/12.1<br>Female, n (%): 12 (63%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: NR<br>Participants (eyes) analyzed for primary study outcomes: 19<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>Note: data are not shown for a third group where participants were randomized to receive flurbiprofen and ATS 4 times a day for 30 days (N = 9)<br><br>**Inclusion criteria**:<br><br>1. KCS patients with or without Sjögren syndrome<br>2. At least 21 years of age<br>3. Schirmer test (without anesthesia) of 7 mm in 5 min or less in at least 1 eye<br>4. Mild superficial punctate keratitis defined as a corneal punctate fluroscein score of +1 in either eye (scale 0 to 3)<br>5. 1 or more moderate dry eye-related symptom including itching, burning, blurred vision, foreign body sensation, dryness, photophobia, and soreness or pain<br><br>**Exclusion criteria**:<br><br>Patients were excluded from the study if they:<br><br>1. had eye injury, infection, non-dry eye ocular inflammation, trauma, or surgery within the previous 6 months;<br>2. received concurrent treatment that could interfere with the interpretation of the study results (systemic corticosteroids, immunosuppressive therapy, etc.);<br>3. had an uncontrolled disease or significant illness; or<br>4. were pregnant or lactating.<br><br>Postmenopausal patients who were on hormonal replacement therapy were also excluded. |

**Avunduk 2003** *(Continued)*

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| | **Baseline comparison**: at the beginning of the study (day 0), no significant difference was detected between groups in terms of any of the parameters studied |
| Interventions | • **FML plus ATS:** topical FML drops 4 times a day plus ATS 4 to 8 times a day in both eyes for 30 days<br>• **Preservative-free ATS:** 4 times a day in both eyes for 30 days<br><br>ATS (Refresh, Allergan Inc, Irvine, CA, USA); FML (Allergan Inc, Irvine, CA, USA), concentration unspecified<br><br>Note: data not shown for a third group (N = 9, 5 females) treated with topical non-steroidal anti-inflammatory drug (NSAID) eyedrops, flurbiprofen (Ocufen, Allergan Inc, Irvine, CA, USA) 4 times a day plus ATS 4 to 8 times a day in both eyes |
| Outcomes | **Time points of primary outcome data collected**:<br><br>**Primary outcomes of the study**:<br>Difference in change from baseline in symptom severity scores on day 30 (for considering power calculation)<br><br>**Other outcomes of the study**:<br><br>1. Schirmer test<br>2. TBUT<br>3. Fluorescein and Rose Bengal staining scores<br>4. Percentages of reactive cells in each impression cytology specimen (Apo 2.7 staining) obtained from the *right* eyes of all participants |
| Study Identification | **Sponsorship Source:** US Public Health Service Grant EY02377 (H.E.K.) from the National Eye Institute, National Institutes of Health, Bethesda, Maryland, and an unrestricted departmental grant from Research to Prevent Blindness Inc, New York, NY<br><br>**Ethics approval:** informed consent was obtained from all participants, and the research was begun after obtaining approval from the Institutional Review Board of the Louisiana State University Health Sciences Center<br><br>**Correspondence author's name:** Avni Murat Avunduk, MD; Institution: KTU (Karadeniz Technical University, Turkish: Karadeniz Teknik Üniversitesi or KTÜ), Konya, Turkey<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

**Bausch 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2013/05 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2014/01 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant |

**Bausch 2013** *(Continued)*

**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: single (investigator)

**05. Study visits and the corresponding time points**: Visit 1 (14 days before randomization), Visit 2 (Day 0, randomization), Visit 3 (Week 4), Visit 4 (Week 12), Visit 5 (Week 13)

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**:

OSDI is a 12-item questionnaire developed to assess severity of DED. There are 3 question types: "Have you experienced any of following (light sensitivity, eye feel gritty, sore eyes, blurred vision, and poor vision) during last week?"(items 1 to 5); "Have problems with your eyes limited you in performing any of following (reading, driving at night, working with computer, and watching TV) during last week?" (items 6 to 9); and "Have your eyes felt uncomfortable in any of following situations (windy, low humidity, air conditioned) during the last week?" (items 10 to 12). Responses to each question were graded on a scale (that relates to the frequency of ocular surface disease effects) of 0 (none of the time) to 4 (all of the time). Total OSDI score was calculated using the following formula: OSDI = ([sum of scores for all questions answered] × 100)/([total number of questions answered] * 4). Total OSDI score ranged from 0 to 100, with higher scores representing greater disability.

Participants scored their degree of comfort with their assigned study drug on a 4-point scale (0 to 3 units) within 5 minutes after instillation of study drug. Comfort grade 0 indicated comfortable, discomfort absent; 1 indicated generally comfortable, mild discomfort; 2 indicated some discomfort but tolerable, moderate discomfort; 3 indicated severely uncomfortable or intolerable. The mean global ocular comfort grade was reported.

**07. Assessment for safety outcomes**: an AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious AEs were defined as death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition.

**08. Planned follow-up duration**: 13 weeks

**09. Actual follow-up duration**: 13 weeks

**10. Planned treatment duration (of the intervention steroid)**: 12 weeks

**11. How missing data were handled**: imputation using mixed-effect model for repeated measures (MMRM) method

**12. Description of power and sample size calculation**: NR

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Participants

**Country**: USA

**Setting**: single medical center

**Interventions**:

- **Loteprednol etabonate (LE) gel 0.5% and cyclosporine A (CsA) 0.05% plus Soothe**

Age, mean/SE (range): 62.0/8.30
Female, n (%): 25 (76%)
Etiology, n (%): NR
Participants (eyes) randomized: 33
Participants (eyes) analyzed for primary study outcomes: 32
Participants (eyes) analyzed for safety outcomes: 33

- **Loteprednol etabonate (LE) gel 0.5% plus Soothe**

Age, mean/SE (range): 64.3/9.1
Female, n (%): 30 (83%)
Etiology, n (%): NR

**Bausch 2013** *(Continued)*

Participants (eyes) randomized: 33
Participants (eyes) analyzed for primary study outcomes: 32
Participants (eyes) analyzed for safety outcomes: 33

- **Cyclosporine A (CsA) 0.05% plus Soothe**

Age, mean/SE (range): 61.6/9.98
Female, n (%): 26 (79%)
Etiology, n (%): NR
Participants (eyes) randomized: 36
Participants (eyes) analyzed for primary study outcomes: 36
Participants (eyes) analyzed for safety outcomes: 36

- **Overall**

Age, mean/SE (range): 62.7/9.1
Female, n (%): 81 (79%)
Etiology, n (%): NR
Participants (eyes) randomized: 102
Participants (eyes) analyzed for primary study outcomes: 101
Participants (eyes) analyzed for safety outcomes: 102

**Inclusion criteria**:

1. Have been diagnosed with or treated for keratoconjunctivitis sicca (DED) within 6 months prior to screening visit (day −14)
2. Have a baseline IOP measurement of ≥ 5 mmHg and ≤ 22 mmHg in each eye, with or without antiglaucoma therapy
3. Have mild to moderate DED in 1 eye or both eyes at screening visit (day −14) and randomization visit (day 0)

**Exclusion criteria**:

1. Have a known hypersensitivity to corticosteroids, ciclosporin, fluorescein, Lissamine green, topical anesthetic, or any component of either of the study drugs
2. Have severe DED
3. Have corneal erosive disease or other conditions suggestive of extensive damage of the cornea
4. Have a history of elevated IOP, a history of glaucoma, or IOP > 22 mmHg in either eye at the screening visit (day −14)
5. Have had penetrating intraocular surgery in the past 12 months or require penetrating intraocular surgery during the study
6. Have had eyelid surgery within the 6 months prior to Visit 1 (Day −14) or have DED secondary to surgery
7. Have visible evidence of anterior lid *Demodex* spp. infection or infestation
8. Have had corneal refractive surgery or corneal transplantation
9. Have congenitally absent lacrimal or meibomian glands or have any obstructive disease of the lacrimal glands, sarcoidosis, or any other lacrimal gland deficiency
10. Have a diagnosis of ongoing ocular infection, active anterior blepharitis, moderate to severe pinguecula, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, significant conjunctival scarring, ocular chemical burn, or ocular neurotrophic keratitis
11. Have any serious systemic disease or uncontrolled medical condition that in the judgement of the investigator could confound study assessments or limit compliance
12. Have a history of ocular herpetic keratitis or have had active blepharitis in the 4 weeks prior to the first dose
13. Have had ocular surgery (including laser) within 6 months prior to the first Treatment Period, or plan or require ocular surgery during the study. Neodymiumdoped:yttrium aluminum garnet (Nd:YAG) laser posterior capsulotomy is allowed.

**Baseline comparison**: no differences in age or sex distribution among the three comparison groups

| Interventions |
|---|

**Bausch 2013** *(Continued)*

- **Loteprednol etabonate (LE) gel 0.5% and cyclosporine A (CsA) 0.05% plus Soothe**, LE gel 0.5% twice per day in both eyes for 2 weeks, then administer both LE gel 0.5% and CsA emulsion 0.05% twice per day in both eyes for 2 weeks, then administer CsA emulsion 0.05% twice per day in both eyes for 8 weeks
  - LE run-in before adding CsA
- **LE gel 0.5% plus Soothe**, twice per day for 12 weeks
- **CsA 0.05% plus Soothe**, twice per day for 12 weeks

| | |
|---|---|
| Outcomes | **Time points of primary outcome data collected**: at week 4<br><br>**Primary outcomes of the study**:<br><br>1. Change from baseline in mean corneal total fluorescein staining score for the study eye at week 4 [ Time frame: baseline (Day 0), week 4 ]<br>2. Change from baseline in mean OSDI questionnaire total score at week 4 [ Time frame: baseline, week 4 ]<br>3. Percentage of participants with adverse events [ Time frame: baseline up to week 13 ]<br>4. Mean grade for participant-reported post-dosing ocular comfort values [ Time frame: week 12 ]<br><br>**Other outcomes of the study**:<br><br>1. Change from baseline in mean OSDI questionnaire total score and individual score at week 12<br>2. Change from baseline in mean corneal total fluorescein staining score for both eyes at week 12<br>3. Change from baseline in mean value of participant worst eye score for each symptom (including the prespecified worst symptom) in the list of possible worst symptoms at week 12<br>4. Change from baseline in mean total combined Lissamine green staining (nasal plus temporal conjunctival) score for the study eye and averaged for both eyes at week 12<br>5. Change from baseline in mean tear osmolarity of participant worst eye value at week 12<br>6. Change from baseline in mean tear osmolarity between 2 eyes of participant at week 12<br>7. Change from baseline in mean eye comfort index questionnaire total score and individual question scores at week 12<br>8. Change from baseline in mean eye dryness questionnaire total and individual question scores at week 12<br>9. Change from baseline in mean TBUT (by fluorescein staining) of the study eye and averaged for both eyes of a participant at week 1<br>10. Change from baseline in mean NIKBUT of the study eye and averaged for both eyes of a participant at week 12<br>11. Change from baseline in mean anesthetized Schirmer's test values (distance of strips wetting) in the study eye and averaged for both eyes of a participant at week 13—averaged daily soothe lubricant eye drops usage<br>12. Number of participants with overall change from baseline in dry symptoms at week 12 as assessed independently by investigators and participants<br>13. Change from baseline in ocular redness score for study eye and averaged for both eyes at week 12, as assessed by investigator<br>14. Change from baseline in non-invasive keratographic limbal and bulbar ocular redness scores for study eye and averaged for both eyes at week 12, as assessed by investigator |
| Study Identification | **Sponsorship Source:** Bausch & Lomb Inc<br><br>**Ethics approval:** NR (on ClinicalTrials.gov)<br><br>**Correspondence author's name:** Susan Harris; Institution: Bausch Health Americas Inc<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT01817582<br>2. Trial registration website: ClinicalTrials.gov |

**Bausch 2013** *(Continued)*

3. Financial disclosure or conflicts of interest statement from authors: NR

Notes

**Byun 2012**

***Study characteristics***

Methods

**00. Study design:** randomized controlled trial, parallel group

**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR

**02. Calendar time when the study completed follow-up** (YYYY/MM): NR

**03. Unit of randomization (participant or eye)**: participant

**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR

**05. Study visits and the corresponding time points**: baseline, month 1, 2, 3

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: patient-reported symptom scores: according to a scoring system ranging from 0 (absent) to 4 (severe) in terms of 6 ocular surface symptoms: burning, itching, foreign body sensation, blurring, photophobia, and pain. A total score was obtained by adding the scores for each symptom, and this was considered in the evaluation of overall ocular discomfort.

**07. Assessment for safety outcomes**: instillation site disorders such as burning, stinging, conjunctival hyperemia, and bitter taste

**08. Planned follow-up duration**: 3 months

**09. Actual follow-up duration**: 3 months

**10. Planned treatment duration (of the intervention steroid)**: 3 weeks before tapering off

**11. How missing data were handled**: complete-case analysis

**12. Description on power and sample size calculation**: NR

Participants

**Country**: Republic of Korea

**Setting**: single-site, university-affiliated eye center

**Interventions**:

- **Methylprednisolone 1% plus cyclosporine A 0.05%**

Age, mean/SD (range): 51.2/14.0
Female, n (%): 18 (86%)
Etiology, n (%): NR
Participants (eyes) randomized: 21
Participants (eyes) analyzed for primary study outcomes: 21
Participants (eyes) analyzed for safety outcomes: 21

- **Cyclosporine A 0.05%**

Age, mean/SD (range): 52.2/9.4
Female, n (%): 17 (74%)
Etiology, n (%): NR
Participants (eyes) randomized: 23
Participants (eyes) analyzed for primary study outcomes: 20
Participants (eyes) analyzed for safety outcomes: 23

**Byun 2012** *(Continued)*

- **Overall**

Age, mean/SD (range): 51.7/11.7
Female, n (%): 35 (80%)
Etiology, n (%): NR
Participants (eyes) randomized: 44
Participants (eyes) analyzed for primary study outcomes: 41
Participants (eyes) analyzed for safety outcomes: 44

**Inclusion criteria**:

1. Dry eye symptoms for > 6 months
2. Low TBUT (< 5 s)
3. Low Schirmer scores (< 7 mm/5 min)
4. Positive corneal and conjunctival fluorescein staining

**Exclusion criteria**:

1. The presence of any ocular disease other than dry eye
2. Use of contact lenses, presence of uncontrolled systemic diseases other than Sjögren's syndrome
3. Corneal disorders affecting sensitivity
4. Severe goblet cell dysfunction

**Baseline comparison**: groups 1 and 2 were similar in terms of pretreatment (baseline) signs and symptoms (Table 1)

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|---|---|
| Interventions | • **Methylprednisolone (MP) 1% plus cyclosporine A (CsA) 0.05%**, 4 times a day for the first week, 3 times a day for the second week, 2 times a day for the third week, and then tapered off; CsA 2 times daily for 3 months<br>  ○ MP run-in concurrently with CsA<br>• **Cyclosporine A (CsA) 0.05%**, 2 times daily for 3 months |
| Outcomes | **Time points of primary outcome data collected**: at month 1, 2, 3<br><br>**Primary outcomes of the study**:<br><br>1. Subjective symptoms<br>2. Objective evaluations: TBUT, Schirmer's I test, cornea and conjunctival staining based on NEI Workshop Report grid system<br>3. Proinflammatory factors: IL-6, IL-8 concentration in tears<br><br>**Other outcomes of the study**:<br><br>1. Frequency of artificial tear use (times per day) |
| Study Identification | **Sponsorship Source**: supported by the Dong-A University Research Fund in 2007, and partially supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST No. 2009-0066392)<br><br>**Ethics approval**: all applicable institutional regulations concerning the ethical use of human volunteers were followed during this research (IRB no. 4-2006-0141)<br><br>**Correspondence author's name:** Woo Chan Park; Institution: Department of Ophthalmology, Dong-A University College of Medicine<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: the authors have no proprietary interests in any of the products discussed in this manuscript |

**Byun 2012** *(Continued)*

Notes

**Cao 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): NR<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR<br><br>**05. Study visits and the corresponding time points**: baseline, week 2 and 6<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: NA<br><br>**07. Assessment for safety outcomes**: complications and ocular discomfort (irritation or sticky sensation)<br><br>**08. Planned follow-up duration**: 6 weeks<br><br>**09. Actual follow-up duration**: 6 weeks<br><br>**10. Planned treatment duration (of the intervention steroid)**: 6 weeks<br><br>**11. How missing data were handled**: NA<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country**: China<br><br>**Setting**: single medical center<br><br>**Intervention**:<br><br>• **Loteprednol plus sodium hyaluronate**<br><br>Age, mean/SD (range): NR<br>Female, n (%): NR<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 64<br>Participants (eyes) analyzed for primary study outcomes: 64<br>Participants (eyes) analyzed for safety outcomes: 64<br><br>• **Sodium hyaluronate 1 g/L**<br><br>Age, mean/SD (range): NR<br>Female, n (%): NR<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 64<br>Participants (eyes) analyzed for primary study outcomes: 64<br>Participants (eyes) analyzed for safety outcomes: 64<br><br>• **Overall**<br><br>Age, mean/SD (range): 7.8/3.3 (3 to 14)<br>Female, n (%): 70 (54.7%) |

**Cao 2018** *(Continued)*

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|---|---|
| | Etiology, n (%): NR<br>Participants (eyes) randomized: 128<br>Participants (eyes) analyzed for primary study outcomes: 128<br>Participants (eyes) analyzed for safety outcomes: 128<br><br>**Inclusion criteria**:<br><br>Dry eye symptoms: frequent blinking, fatigue sensation, dryness, burning, itchiness, photophobia, redness, and at least 1 of the following signs: TBUT ≤ 5 s, or TBUT > 5 s but ≤ 10 s; corneal staining score > 3 points; tear meniscus height < 0.3 mm<br><br>**Exclusion criteria**:<br><br>1. Glaucoma or corneal insufficiency, anterior segment inflammatory disorders<br>2. Lacrimal duct obstruction<br>3. Exophthalmos<br>4. Systemic diseases<br>5. History of allergy to medications<br><br>**Baseline comparison**: NR |
| Interventions | • **Loteprednol plus sodium hyaluronate**, 4 times a day for 6 weeks<br>• **Sodium hyaluronate 1 g/L**, 4 times a day for 6 weeks |
| Outcomes | **Time points of primary outcome data collected**: week 2, 6<br><br>**Primary outcomes of the study**:<br><br>1. TBUT<br>2. Schirmer's test<br>3. Tear meniscus height<br>4. Meibomian gland infrared photography<br>5. Corneal fluorscein staining<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source:** NR<br><br>**Ethics approval**: this study was approved by the institutional review board of the hospital<br><br>**Correspondence author's name:** Xian-Yong Cao; Institution: The Third Affiliated Hospital of Xinxiang Medical University, Henan, China<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

**Chen 2020**

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|---|---|
| ***Study characteristics*** | |

**Chen 2020** *(Continued)*

| | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2018/07<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2019/06<br><br>**03. Unit of randomization (participant or eye)**: participant (the worst eye or the right eye)<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR<br><br>**05. Study visits and the corresponding time points**: before and after treatment<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: SPEED questionnaire: according to the frequency of symptoms, dry eye was divided into 4 grades (I: 0 score; II: 1 score; III: 2 scores; IV: 3 scores). The total score is calculated by adding the scores of the 4 symptoms (dryness, foreign body sensation, burning sensation, and eye irritation). The maximum is 12 scores. A total score < 10 points is the mild symptom group, and > 10 points is the severe symptom group.<br><br>**07. Assessment for safety outcomes**: NR<br><br>**08. Planned follow-up duration**: NR<br><br>**09. Actual follow-up duration**: NR<br><br>**10. Planned treatment duration (of the intervention steroid)**: 1 month<br><br>**11. How missing data were handled**: NA<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country**: China<br><br>**Setting**: single-site, university-affiliated eye center<br><br>**Interventions**:<br><br>• **Loteprednol 0.1% combined with sodium hyaluronate 0.1%**<br><br>Age, mean/SD (range): 47.4/11.0<br>Female, n (%): 72 (87%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 83<br>Participants (eyes) analyzed for primary study outcomes: 83<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Sodium hyaluronate 0.1%**<br><br>Age, mean/SD (range): 51.1/11.8<br>Female, n (%): 68 (82%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 83<br>Participants (eyes) analyzed for primary study outcomes: 83<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Overall**<br><br>Age, mean/SD (range): 49.2/11.5<br>Female, n (%): 140 (84%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 166<br>Participants (eyes) analyzed for primary study outcomes: 166<br>Participants (eyes) analyzed for safety outcomes: NR |

**Chen 2020** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria**: dry eye patients and people who received simple optometry with glasses in the ophthalmic outpatient department<br><br>**Exclusion criteria**: NR<br><br>**Baseline comparison**: as shown in Table I, the differences of age and gender between the 3 groups were not significant (P > 0.05, Table I) |
| Interventions | • **Loteprednol 0.1% combined with sodium hyaluronate 0.1%**, dosing schedule NR<br>• **Sodium hyaluronate 0.1%**, dosing schedule NR |
| Outcomes | **Time points of primary outcome data collected**: before and after treatment<br><br>**Primary outcomes of the study**:<br><br>1. Dry eye symptom<br>2. TBUT<br>3. Tear secretion test (Schirmer I test)<br>4. Corneal fluorescein staining score<br>5. Expression of TNF-α and CXCL10 in tears<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source:** this study was supported by grants from the National Natural Science Foundation of China (NSFC no. 81970771), Huaxia Translation Medicine Funding (no. 2017-A-02), Xiamen Key Medical and Health Project (no.3502Z20191101), and Zhenjiang Science Technology Planning. Project (No. SH2019033)<br><br>**Ethics approval**: the experimental protocol was reviewed and approved by the Ethics Committee of Xiamen University Medical College. All participants were informed of the purpose of this study and signed informed consent.<br><br>**Correspondence author's name**: Nuo Dong, MD; Institution: Department of Ophthalmology, Affiliated People's Hospital & Zhenjiang Kangfu Eye Hospital, Jiangsu University, Jiangsu, China<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

**KPI-121 (Phase 2)**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2014/06 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2015/01 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: quadruple masking (participant, care provider, investigator, outcomes assessor) |

**KPI-121 (Phase 2)** *(Continued)*

**05. Study visits and the corresponding time points**: 6 visits: Visit 1 Screening (14 ± 1 days prior to Day 1), Visit 2 Randomization (Day 1), Visit 3 (Days 8 ± 1), Visit 4 (Day 15 ± 1), Visit 5 (Day 22 ± 1), Visit 6 (Day 29 ± 1)

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: visual analog grading scale (OSDI) for ocular discomfort

**07. Assessment for safety outcomes**: adverse events, slit lamp biomicroscopy, IOP measurement, BCVA

**08. Planned follow-up duration**: 29 days

**09. Actual follow-up duration**: 29 days

**10. Planned treatment duration (of the intervention steroid)**: 28 days

**11. How missing data were handled**: NA

**12. Description on power and sample size calculation**: descriptions about power and sample size calculation were partially blocked in the publicly available trial protocol

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Participants

**Country**: USA

**Setting**: eye clinics at medical centers and private medical groups

**Interventions**:

- **KPI-121 (loteprednol etabonate 0.25%)**

Age, mean/SD (range): 56.3/17.2
Female, n (%): 53 (73%)
Etiology, n (%): NR
Participants (eyes) randomized: 73
Participants (eyes) analyzed for primary study outcomes: 73
Participants (eyes) analyzed for safety outcomes: 72

- **Vehicle of KPI-121**

Age, mean/SD (range): 54.9/12.3
Female, n (%): 61 (79%)
Etiology, n (%): NR
Participants (eyes) randomized: 77
Participants (eyes) analyzed for primary study outcomes: 77
Participants (eyes) analyzed for safety outcomes: 78

- **Overall**

Age, mean/SD (range): 55.6/14.8
Female, n (%): 114 (76%)
Etiology, n (%): NR
Participants (eyes) randomized: 150
Participants (eyes) analyzed for primary study outcomes: 150
Participants (eyes) analyzed for safety outcomes: 150

Note: 1 participant was randomized to KPI-121 0.25% but received vehicle. As a result, 72 participants are included in the KPI-121 0.25% group, and 78 participants are included in the vehicle group in the safety analyses.

**Inclusion criteria**:

1. 18 years of age or older
2. Have a documented clinical diagnosis of dry eye disease in both eyes
3. Have ongoing dry eye disease as defined by the following criteria in the same eye or both eyes:

**KPI-121 (Phase 2)** *(Continued)*

a. a corneal fluorescein staining score at Visit 1 and Visit 2 of [blocked]* (National Eye Institute [NEI] scale); and
b. bulbar conjunctival hyperemia at Visit 1 and Visit 2 of [blocked] as assessed using the Cornea and Contact Lens Research Unit (CCLRU) scale; and
c. a score of [blocked] Severity Assessment at Visit 1 and a score of [blocked] Severity Visit 2 (Day 1); and
d. an unanesthetized Schirmer test score at Visit 1 of [blocked].(more extensive criteria shown in the protocol)

*[blocked] were phrases or words in the study protocol that were blocked from viewing

**Exclusion criteria**:

1. Known hypersensitivity/contraindication to study product(s) or components
2. History of glaucoma, IOP > 21 mmHg at the screening or randomization visits, or being treated for glaucoma in either eye
3. Diagnosis of: ongoing ocular infection; severe/serious ocular condition that in judgement of Investigator could confound study assessments or limit compliance; severe/serious systemic disease or uncontrolled medical condition that in judgement of Investigator could confound study assessments or limit compliance; or have been exposed to an investigational drug within the 30 days prior to screening
4. In the opinion of Investigator or study co-ordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eye drops (more criteria shown in the protocol)

**Baseline comparison**: no significant differences in baseline characteristics between groups (source: ClinicalTrials.gov)

| | |
|---|---|
| Interventions | • **KPI-121 (loteprednol etabonate 0.25%)**, 4 times a day for 28 days<br>• **Vehicle for KPI-121,** 4 times a day for 28 days |
| Outcomes | **Time points of primary outcome data collected**: Visit 6 (Day 29)<br><br>**Primary outcomes of the study**:<br><br>1. Bulbar conjunctival hyperemia; the grading scale was based on the Cornea and Contact Lens Research Unit Grading Scale, where 0 = none, 1 = very slight, 2 = slight, 3 = moderate, and 4 = severe<br>2. Ocular discomfort on a 0-to-100 VAS (0 was better and 100 was worse) at Visit 6 (Day 29)<br><br>**Other outcomes of the study**:<br><br>1. Corneal fluorescein staining scores at Visit 4 (Day 15) and Visit 6 (Day 29)<br>2. Bulbar conjunctival hyperemia scores at Visit 4 (Day 15)<br>3. Ocular discomfort at Visit 4 (Day 15) |
| Study Identification | **Sponsorship Source**: Kala Pharmaceuticals Inc<br><br>**Ethics approval**: IRB approval was required by the study protocol, but no specific institutional review boards were mentioned in the protocol or in the prescribing information<br><br>**Correspondence author's name:** NR<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT021881600<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: NR |

**KPI-121 (Phase 2)** *(Continued)*

| | |
|---|---|
| Notes | 78% of study participants were white. |

**KPI-121 (STRIDE1)**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2016/06 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2017/10 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: quadruple (participant, care provider, investigator, outcomes assessor)<br><br>**05. Study visits and the corresponding time points**:<br>Visit 1 (14 ± 1 days before Visit 2) for screening<br>Visit 2 (Day 1) for randomization<br>Visit 3 (Day 8 ± 1)<br>Visit 4 (Day 15 ± 1)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: participant-rated assessment of ocular discomfort [blocked]* utilizing [blocked] VAS (0 to 100)<br><br>**07. Assessment for safety outcomes**: adverse events; slit lamp biomicroscopy; IOP measurement; BCVA<br><br>**08. Planned follow-up duration**: 15 days<br><br>**09. Actual follow-up duration**: 15 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 14 days<br><br>**11. How missing data were handled**: complete-case analysis<br><br>**12. Description on power and sample size calculation**: descriptions about power and sample size calculation were partially blocked in the publicly available trial protocol |
| Participants | **Country**: USA<br><br>**Setting**: multicenter<br><br>**Interventions**:<br><br>• **KPI-121 (loteprednol etabonate 0.25%)**<br><br>Age, mean/SD (range): 58.1/15.4<br>Female, n (%): 367 (80.0%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 459<br>Participants (eyes) analyzed for primary study outcomes: 452/455<br>Participants (eyes) analyzed for safety outcomes: 459<br><br>• **Vehicle of KPI-121**<br><br>Age, mean/SD (range): 58.3/14.7<br>Female, n (%): 359 (78.7%)<br>Etiology, n (%): NR |

**KPI-121 (STRIDE1)** *(Continued)*

Participants (eyes) randomized: 456
Participants (eyes) analyzed for primary study outcomes: 451/452
Participants (eyes) analyzed for safety outcomes: 456

- **Overall**

Age, mean/SD (range): 58.2/15.0
Female, n (%): 726 (79.3%)
Etiology, n (%): NR
Participants (eyes) randomized: 915
Participants (eyes) analyzed for primary study outcomes: 903/907
Participants (eyes) analyzed for safety outcomes: 915

**Inclusion criteria**:

1. 18 years of age or older
2. Have a documented clinical diagnosis of dry eye disease in both eyes
3. Have ongoing dry eye disease as defined by the following criteria in the same eye or both eyes:
   a. a corneal fluorescein staining score at Visit 1 and Visit 2 of [blocked]* (National Eye Institute [NEI] scale); and
   b. bulbar conjunctival hyperemia at Visit 1 and Visit 2 of [blocked] as assessed using the Cornea and Contact Lens Research Unit (CCLRU) scale; and
   c. a score of [blocked] Severity Assessment at Visit 1 and a score of [blocked] Severity Visit 2 (Day 1); and
   d. an unanesthetized Schirmer test score at Visit 1 of [blocked]. (more criteria shown in the study protocol)

*[blocked] were phrases or words in the study protocol that were blocked from viewing

**Exclusion criteria**:

1. Have a known hypersensitivity or contraindication to the investigational product(s) or their components
2. Have used any of the following medications within 30 days prior to Screening (Visit 1) or for the duration of the study:
   a. ocular, inhaled, or intranasal corticosteroids;
   b. ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs), with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin);
   c. topical ocular antibiotics;
   d. topical ocular antihistamines or mast cell stabilizers;
   e. oral antihistamines;
   f. topical or nasal vasoconstrictors.
3. Have used any of the following medications within 60 days prior to Screening (Visit 1) or for the duration of the study: topical ciclosporin (Restasis), topical lifitegrast, any form of topical loteprednol etabonate
4. Have altered oral dosing of the following within 30 days prior to Screening (Visit 1) or anticipate alteration of dosing during the study:
   a. tetracycline compounds (e.g. tetracycline, doxycycline, or minocycline);
   b. Omega-3 or Omega-6 supplements.
5. Have altered dosing of the following medications within 6 months prior to Screening (Visit 1) or anticipate alteration of dosing during the study:
   a. anticholinergics;
   b. anticonvulsants (e.g. topiramate);
   c. antidepressants;
   d. isotretinoin;
   e. systemic immunosuppressive agents including oral corticosteroids at a dose of prednisone < 11 mg/day or equivalent.

**KPI-121 (STRIDE1)** *(Continued)*

| | |
|---|---|
| | NOTE: oral corticosteroid use at a dose of prednisone > 11 mg/day or equivalent is excluded. (more criteria shown in the study protocol)<br><br>**Baseline comparison**: no significant differences in baseline characteristics between groups (source: ClinicalTrials.gov) |
| Interventions | • **KPI-121 (loteprednol etabonate 0.25%)**, 4 times a day for 14 days<br>• **Vehicle for KPI-121,** 4 times a day for 14 days |
| Outcomes | **Time points of primary outcome data collected**: change from Visit 2 (Day 1) to Visit 4 (Day 15)<br><br>**Primary outcomes of the study**:<br><br>1. Change from baseline/Visit 2 (Day 1) in bulbar conjunctival hyperemia at Visit 4 (Day 15)<br>2. Change from baseline/Visit 2 (Day 1) in ocular discomfort severity at Visit 4 (Day 15)<br>3. Change from baseline/Visit 2 (Day 1) in corneal fluorescein staining score at Visit 4 (Day 15)<br>4. Change from baseline/Visit 2 (Day 1) ocular discomfort severity at Visit 4 (Day 15) in the subgroup of participants with more severe ocular discomfort<br><br>**Other outcomes of the study**:<br><br>1. Change in conjunctival hyperemia scores at Visit 4 (Day 15) in the subgroup of participants with more severe ocular discomfort at baseline (Day 1)<br>2. Proportion of participants with ≥1 improvement in conjunctival hyperemia at Visit 4 (Day 15)<br>3. Change from baseline/Visit 2 (Day 1) conjunctival hyperemia scores at Visit 4 (Day 15) for the mean of all regions (nasal, temporal, frontal)<br>4. Change in ocular discomfort severity scores prior to Visit 3 (Day 8) minus the mean of the scores to baseline/Visit 2 (Day 1)<br>5. Change in ocular discomfort severity scores prior to Visit 3 (Day 8) minus baseline/Visit 2 (Day 1) in the subgroup of participants with more severe ocular discomfort<br>6. Change in ocular discomfort severity scores on Day 4 (Diary) minus baseline/Visit 2 (Day 1)<br>7. Change in ocular discomfort severity scores on Day 4 (Diary) minus baseline/Visit 2 (Day 1) in the subgroup of participants with more severe ocular discomfort<br>8. Change from baseline/Visit 2 (Day 1) in conjunctival hyperemia scores with a Day 1 conjunctival hyperemia score of ≥ 2 in the subgroup of participants with more severe ocular discomfort<br>9. Participants with a grade of 0 in conjunctival hyperemia score at Visit 4 (Day 15) |
| Study Identification | **Sponsorship source:** Kala Pharmaceuticals Inc<br><br>**Ethics approval**: the study protocol states that: "This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the sponsor or designee prior to the start of enrollment into the study based on these items"<br><br>**Correspondence author's name:** NR<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT02813265 (other study ID: KPI-121-C-006)<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | 79% of participants were white. |

**KPI-121 (STRIDE2)**

| *Study characteristics* | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2016/06 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2017/09 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: quadruple (participant, care provider, investigator, outcomes assessor)<br><br>**05. Study visits and the corresponding time points**:<br>Visit 1 (14 ± 1 days before Visit 2) for screening<br>Visit 2 (Day 1) for randomization<br>Visit 3 (Day 8 ± 1)<br>Visit 4 (Day 15 ± 1)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: participant-rated assessment of ocular discomfort [blocked]* utilizing [blocked] VAS (0 to 100).<br>*[blocked] were phrases or words in the study protocol that were blocked from viewing<br><br>**07. Assessment for safety outcomes**: adverse events; slit lamp biomicroscopy; IOP measurement; BCVA<br><br>**08. Planned follow-up duration**: 15 days<br><br>**09. Actual follow-up duration**: 15 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 14 days<br><br>**11. How missing data were handled**: complete-case analysis<br><br>**12. Description on power and sample size calculation**: (same as in the study protocol for STRIDE 1) |
| Participants | **Country:** USA<br><br>**Setting:** multicenter<br><br>**Interventions:**<br><br>• **KPI-121 (loteprednol etabonate 0.25%)**<br><br>Age, mean/SD (range): 59.1/14.5<br>Female, n (%): 332 (73.5%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 452<br>Participants (eyes) analyzed for primary study outcomes: 445/446<br>Participants (eyes) analyzed for safety outcomes: 452<br><br>• **Vehicle of KPI-121**<br><br>Age, mean/SD (range): 59.3/15.0<br>Female, n (%): 354 (78.1%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 453<br>Participants (eyes) analyzed for primary study outcomes: 444/447<br>Participants (eyes) analyzed for safety outcomes: 453<br><br>• **Overall**<br><br>Age, mean/SD (range): 59.2/14.7 |

**KPI-121 (STRIDE2)** *(Continued)*

Female, n (%): 686 (75.8%)
Etiology, n (%): NR
Participants (eyes) randomized: 905
Participants (eyes) analyzed for primary study outcomes: 889/893
Participants (eyes) analyzed for safety outcomes: 905

**Inclusion criteria**: (same study protocol for STRIDE 1)

**Exclusion criteria**: (same study protocol for STRIDE 1)

**Baseline comparison**: no significant differences in baseline characteristics between groups (source: ClinicalTrials.gov)

Interventions

- **KPI-121 (loteprednol etabonate 0.25%)**, 4 times a day for 14 days
- **Vehicle for KPI-121,** 4 times a day for 14 days

Outcomes

**Time points of primary outcome data collected**: baseline/visit 2 (day 1) and visit 4 (day 15)

**Primary outcomes of the study**:

1. Change from baseline/visit 2 (day 1) in bulbar conjunctival hyperemia at visit 4 (day 15)
2. Change from baseline/visit 2 (day 1) in ocular discomfort severity at visit 4 (day 15)

**Other outcomes of the study**:

1. Proportion of participants with ≥ 1 unit improvement from baseline/visit 2 (day 1) in bulbar conjunctival hyperemia worst region at visit 4 (day 15)
2. Change from baseline/visit 2 (day 1) in ocular discomfort severity scores at visit 3 (day 8)
3. Change from baseline/week 2 (day 1) in ocular discomfort scores to day 4
4. Change from baseline/week 2 (day 1) in ocular discomfort severity at visit 4 (day 15) in a subgroup
5. Change from baseline/visit 2 (day 1) in ocular discomfort severity scores at day 3 (diary)
6. Change from baseline/visit 2 (day 1) in eye dryness scores at visit 4 (day 15)
7. Change from baseline/visit 2 (day 1) in eye dryness scores at visit 3 (day 8)
8. Ocular discomfort severity scores on day 2 (diary) minus baseline/visit 2 (day 1)
9. Change from baseline/visit 2 (day 1) in ocular discomfort frequency scores at visit 4 (day 15)—change from baseline/visit 2 (day 1) in participant-rated ocular discomfort frequency scores at visit 3 (day 8)
10. Change from baseline/visit 2 (day 1) in inferior corneal fluorescein staining score at visit 4 (day 15)
11. Change from baseline/visit 2 (day 1) in nasal corneal fluorescein staining score at visit 4 (day 15)

Study Identification

**Sponsorship source:** Kala Pharmaceuticals Inc

**Ethics approval:** the study protocol states that: "This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the sponsor or designee prior to the start of enrollment into the study based on these items"

**Correspondence author's name:** NR

**Additional information:**

1. Trial registration no.: NCT02819284 (other study ID KPI-121-C-007)
2. Trial registration website: ClinicalTrials.gov
3. Financial disclosure or conflicts of interest statement from authors: NR

Notes

- 77% of participants were white.

**KPI-121 (STRIDE2)** *(Continued)*

- Both treatment-related and non-treatment-related adverse events were reported together.

**KPI-121 (STRIDE3)**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2018/07 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2020/02 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: quadruple (participant, care provider, investigator, outcomes assessor)<br><br>**05. Study visits and the corresponding time points**:<br>Visit 1 (14 ± 1 days before Visit 2) for screening<br>Visit 2 (Day 1) for randomization<br>Visit 3 (Day 8 ± 1)<br>Visit 4 (Day 15 ± 1)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: participant-rated assessment of ocular discomfort [blocked]* utilizing [blocked] VAS (0 to 100).<br>*[blocked] were phrases or words in the study protocol that were blocked from viewing<br><br>**07. Assessment for safety outcomes**: adverse events; slit lamp biomicroscopy; IOP measurement; BCVA; dilated ophthalmoscopy; pregnancy screen (performed only at Visits 1 and 4)<br><br>**08. Planned follow-up duration**: 15 days<br><br>**09. Actual follow-up duration**: 15 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 14 days<br><br>**11. How missing data were handled**: complete-case analysis<br><br>**12. Description on power and sample size calculation**: (same as in the study protocol for STRIDE 1 for ocular discomfort severity overall and in subgroup) |
| Participants | **Country:** USA<br><br>**Setting:** multicenter<br><br>**Interventions:**<br><br>• **KPI-121 (loteprednol etabonate 0.25%)**<br><br>Age, mean/SD (range): 57.6/15.3<br>Female, n (%): 339 (75.8%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 447<br>Participants (eyes) analyzed for primary study outcomes: 434<br>Participants (eyes) analyzed for safety outcomes: 449<br><br>• **Vehicle of KPI-121**<br><br>Age, mean/SD (range): 57.3/15.5 |

**KPI-121 (STRIDE3)** *(Continued)*

Female, n (%): 330 (72.7%)
Etiology, n (%): NR
Participants (eyes) randomized: 454
Participants (eyes) analyzed for primary study outcomes: 451
Participants (eyes) analyzed for safety outcomes: 452

- **Overall**

Age, mean/SD (range): 57.4/15.4
Female, n (%): 669 (74.3%)
Etiology, n (%): NR
Participants (eyes) randomized: 901
Participants (eyes) analyzed for primary study outcomes: 885
Participants (eyes) analyzed for safety outcomes: 901

Note: 2 participants were randomized to vehicle (and were included in the vehicle arm for efficacy analyses as part of the ITT population) but erroneously received KPI-121 (and were included in the KPI-121 treatment arm for safety analyses).

**Inclusion criteria**: are willing and able to follow instructions and can be present for the required study visits for the duration of the study, including:

1. single-masked investigational product use compliance of at least 80% during the final week of Stage 1 [blocked]*; and
2. [blocked].(others same as in the study protocol for STRIDE 1)

*[blocked] were phrases or words in the study protocol that were blocked from viewing

**Exclusion criteria**:

1. Have used any of the following medications or had any of the following procedures within 30 days prior to visit 1 (Screening) or for the duration of the study:
   a. ocular, inhaled, or intranasal corticosteroids;
   b. ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin);
   c. topical ocular antibiotics;
   d. topical ocular antihistamines or mast cell stabilizers;
   e. oral antihistamines;
   f. topical or nasal vasoconstrictors;
   g. autologous serum tear preparations;
   h. LipiFlow treatment;
   i. TruTear treatment;
   j. BlephEx treatment.
2. Have used any of the following medications within 60 days prior to visit 1 (Screening) or for the duration of the study: topical ciclosporin (Restasis), topical lifitegrast, any form of topical loteprednol etabonate
3. Be unwilling to abstain from the use of any topical ophthalmic medications at visit 1 (Screening) and for the duration of the study, including:
   a. eyelash growth medications, including both prescription and over-the-counter;
   b. eye drops, gels, ointments, or artificial tears;
   c. TNF-blocking agents.
4. Be currently receiving treatment for glaucoma at visit 1 (Screening) or for the duration of the study and/or have history of or current glaucoma, or an IOP over 21 mmHg at visit 1 (Screening) or visit 2 (Day 1)

(others same as in the study protocol for STRIDE 1)

**Baseline comparison**: no significant differences in baseline characteristics between groups (source: ClinicalTrials.gov)

**KPI-121 (STRIDE3)** *(Continued)*

| | |
|---|---|
| Interventions | • **KPI-121 (loteprednol etabonate 0.25%)**, 4 times a day for 14 days<br>• **Vehicle for KPI-121,** 4 times a day for 14 days |
| Outcomes | **Time points of primary outcome data collected**: baseline/visit 2 (day 1) and visit 4 (day 15)<br><br>**Primary outcomes of the study**:<br><br>1. Change from baseline/visit 2 (day 1) in ocular discomfort severity at visit 4 (day 15)<br>2. Change from baseline/visit 2 (day 1) ocular discomfort severity at visit 4 (day 15) in the subgroup of participants with more severe ocular discomfort<br><br>**Other outcomes of the study**:<br><br>1. Change from baseline/visit 2 (day 1) in bulbar conjunctival hyperemia at visit 4 (day 15)<br>2. Change in conjunctival hyperemia scores at visit 4 (day 15) by alternate assessor<br>3. Change from baseline/visit 2 (day 1) in ocular discomfort severity at visit 3 (day 8)<br>4. Change from baseline/visit 2 (day 1) in corneal fluorescein staining score at visit 4 (day 15)<br>5. Change from baseline/visit 2 (day 1) in ocular discomfort severity at visit 4 (day 15) using 7-day mean |
| Study Identification | **Sponsorship source**: Kala Pharmaceuticals Inc<br><br>**Ethics approval**: the study protocol states that: "This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the Sponsor or designee prior to the start of enrollment into the study based on these items"<br><br>**Correspondence author's name:** NR<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT03616899 (other study ID KPI-121-C-011)<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | 76.5% of participants were white. |

**Lee 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2012/08<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2013/03<br><br>**03. Unit of randomization (participant or eye)**: participant (single eye, the study eye chosen was the one with a higher stage of MGD)<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double-masked (assessor, analyst); physicians and participants were aware of the treatment received<br><br>**05. Study visits and the corresponding time points**: baseline, 1 month, 2 months<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI |

**Lee 2014** *(Continued)*

**07. Assessment for safety outcomes**: safety was assessed by monitoring any adverse events during the entire course of study

**08. Planned follow-up duration**: 2 months

**09. Actual follow-up duration**: 2 months

**10. Planned treatment duration (of the intervention steroid)**: 2 months

**11. How missing data were handled**: complete-case analysis; 4 participants (4 eyes) in group I and 6 participants (6 eyes) in group II were lost to follow-up. Measurements of the remaining 60 eyes of 60 participants were used for statistical analysis.

**12. Description on power and sample size calculation**: the primary outcome measure of this study was inflammatory tear cytokine levels at 2 months after treatment

| | |
|---|---|
| Participants | **Country**: South Korea<br><br>**Setting**: single university-affiliated medical center<br><br>**Interventions**:<br><br>• **Loteprednol etabonate 0.5% and eyelid scrubs with warm compresses**<br><br>Age, mean/SD (range): 66.8/10.1 (46 to 81)<br>Female, n (%): 19 (56%)<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 34<br>Participants (eyes) analyzed for primary study outcomes: 30<br>Participants (eyes) analyzed for safety outcomes: 30<br><br>• **Eyelid scrubs with warm compresses**<br><br>Age, mean/SD (range): 67.1/11.7 (44 to 81)<br>Female, n (%): 20 (56%)<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 36<br>Participants (eyes) analyzed for primary study outcomes: 30<br>Participants (eyes) analyzed for safety outcomes: 30<br><br>• **Overall**<br><br>Age, mean/SD (range): 66.9/10.9<br>Female, n (%): 39 (56%)<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 70<br>Participants (eyes) analyzed for primary study outcomes: 60<br>Participants (eyes) analyzed for safety outcomes: 60<br><br>**Inclusion criteria**:<br><br>1. Stage 3 or 4 MGD<br><br>**Exclusion criteria**:<br><br>1. History of previous ocular or intraocular surgery<br>2. Ocular infection, non-dry eye ocular inflammation, ocular allergy, autoimmune disease<br>3. History of intolerance or hypersensitivity to any component of the study medications<br>4. Wearing contact lenses during the study period, presence of current punctal occlusion<br>5. Pregnancy, lactating women, and children Additionally, patients were excluded if they were using any topical ocular or systemic medication that could be used for the treatment MGD or dry eye, including topical or oral antibiotics, topical cyclosporine A, topical or oral steroids, topical non-steroidal anti-inflammatory drugs (NSAIDs), topical ocular allergy medications, or artificial tears. |

**Lee 2014** *(Continued)*

| | |
|---|---|
| | **Baseline comparison**: no significant differences in any parameters were found between groups before treatment (Table 1) |
| Interventions | • **Loteprednol etabonate 0.5% and eyelid scrubs with warm compresses**, loteprednol 4 times a day following eyelid scrubs with warm compresses 2 times a day for 2 months<br>• **Eyelid scrubs with warm compresses**, 2 times a day for 2 months |
| Outcomes | **Time points of primary outcome data collected**: 2 months<br><br>**Primary outcomes of the study**: inflammatory cytokine levels at 2 months after treatment<br><br>**Other outcomes of the study**: data on both clinical tests and patient-reported outcomes |
| Study Identification | **Sponsorship Source:** Yonsei University<br><br>**Ethics approval:** this randomized controlled trial was prospectively approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (Seoul, South Korea)<br><br>**Correspondence author's name:** Tae-im Kim; Institution: Department of Ophthalmology, Yonsei University College of Medicine, Seoul, South Korea<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT01692652<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: none reported |
| Notes | Continuous outcomes were presented as least square mean (standard error), and P values are from linear mixed model with post hoc analysis considering the interaction effect between the 2 groups and the 3 time courses. Generalized estimating equations model for non-continuous scale values: expressibility, n (%, proportion ≥ grade 1); ocular irritation symptom, n (%, proportion ≥ grade 2); MGD stage, n (%, proportion ≥ stage 3) |

**Li 2021**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2017/02<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2019/12<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double (participant, investigator)<br><br>**05. Study visits and the corresponding time points**: baseline, week 2 and 4<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI<br><br>**07. Assessment for safety outcomes**: participants' tolerability to the treatment ; adverse symptoms<br><br>**08. Planned follow-up duration**: 4 weeks<br><br>**09. Actual follow-up duration**: 4 weeks<br><br>**10. Planned treatment duration (of the intervention steroid)**: 4 weeks |

**Li 2021** *(Continued)*

**11. How missing data were handled**: complete-case analysis

**12. Description on power and sample size calculation**: NR

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|---|---|
| Participants | **Country**: China<br><br>**Setting**: single medical center<br><br>**Interventions**:<br><br>• **Fluorometholone (FML) 0.1% plus hyaluronic acid**<br><br>Age, mean/SD (range): 40.1/8.6<br>Female, n (%): 33 (55%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 60<br>Participants (eyes) analyzed for primary study outcomes: 58<br>Participants (eyes) analyzed for safety outcomes: 58<br><br>• **Hyaluronic acid**<br><br>Age, mean/SD (range): 39.7/9.1<br>Female, n (%): 36 (58%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 62<br>Participants (eyes) analyzed for primary study outcomes: 58<br>Participants (eyes) analyzed for safety outcomes: 58<br><br>• **Overall**<br><br>Age, mean/SD (range): 38.4/9.0<br>Female, n (%): 69 (57%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 122<br>Participants (eyes) analyzed for primary study outcomes: 116<br>Participants (eyes) analyzed for safety outcomes: 116<br><br>**Inclusion criteria**:<br><br>1. Met the diagnostic criteria set by the clinical consensus guidelines (2013)<br>2. Severity of moderate to severe<br>3. Subjective symptoms of dryness, foreign body sensation, burning, fatigue, discomfort<br>4. Objective signs of TBUT < 5 s, Schirmer's test scores < 10 mm/5 min, corneal staining positive<br><br>**Exclusion criteria**: NR<br><br>**Baseline comparison**: there were no statistical differences in pre-treatment characteristics between groups |
| Interventions | • **Fluorometholone (FML) 0.1% plus hyaluronic acid**, 4 times a day for 4 weeks<br>• **Hyaluronic acid**, 4 times a day for 4 weeks |
| Outcomes | **Time points of primary outcome data collected**: week 2 and 4<br><br>**Primary outcomes of the study**:<br><br>1. OSDI<br>2. Schirmer's I test<br>3. TBUT<br>4. Tear meniscus height<br>5. Non-invasive TBUT<br>6. Conjunctival impression cytology |

**Li 2021** *(Continued)*

| | |
|---|---|
| | **Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source**: NR<br><br>**Ethics approval**: NR<br><br>**Correspondence author's name:** Neng Li; Institution: Department of Ophthalmology, Hangzhou Hospital of Traditional Chinese Medicine, Zhejiang, China<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

**Lin 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2013/01<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2013/09<br><br>**03. Unit of randomization (participant or eye)**: participant (the right eye or the worst eye identified by the corneal staining score)<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: open-label (ClinicalTrials.gov)<br><br>**05. Study visits and the corresponding time points**: 14 ± 2, 28 ± 2, and 56 ± 2 days after the first treatment<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI<br><br>**07. Assessment for safety outcomes**: safety was evaluated based on the incidence of adverse events in each treatment group<br><br>**08. Planned follow-up duration**: 8 weeks<br><br>**09. Actual follow-up duration**: 8 weeks<br><br>**10. Planned treatment duration (of the intervention steroid)**: 56 ± 2 days<br><br>**11. How missing data were handled**: complete-case analysis<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country**: China<br><br>**Setting**: single medical center<br><br>**Interventions**:<br><br>• **Fluorometholone (FML) 0.1% plus hyaluronic acid (HA) 0.1%**<br><br>Age, mean/SD (range): 50.4/10.9<br>Female, n (%): NR |

**Lin 2015** *(Continued)*

Etiology, n (%): Sjögren syndrome (100%)
Participants (eyes) randomized: 20
Participants (eyes) analyzed for primary study outcomes: 19
Participants (eyes) analyzed for safety outcomes: 19

- **Cyclosporine A (CsA) 0.5% plus hyaluronic acid (HA) 0.1%**

Age, mean/SD (range): 49.9/10.7
Female, n (%): NR
Etiology, n (%): Sjögren syndrome (100%)
Participants (eyes) randomized: 20
Participants (eyes) analyzed for primary study outcomes: 16
Participants (eyes) analyzed for safety outcomes: 16

- **Overall**

Age, mean/SD (range): 50.2/10.6
Female, n (%): NR
Etiology, n (%): Sjögren syndrome (100%)
Participants (eyes) randomized: 40
Participants (eyes) analyzed for primary study outcomes: 35
Participants (eyes) analyzed for safety outcomes: 35

**Inclusion criteria**:

1. Aged ≥ 18 years
2. Diagnosed with primary or secondary SS, according to the criteria of the American European Consensus Group. Diagnosis was based on a non-anesthetized Schirmer test result of ≤ 5 mm/min, a 1% fluorescein staining score of ≥ 3 out of 12, and the presence of at least 1 of the following autoantibodies in serum: antinuclear antibody, rheumatoid factor, anti-SS-A (Ro), or anti-SS-B (La). A diagnosis of DE required at least 1 of the following DE-related symptoms: dryness, foreign-body sensation, burning, asthenopia, redness, or discharge.

**Exclusion criteria**:
Patients who had suffered an injury or infection to their eye, who had ocular inflammation unrelated to dry eye, who had undergone ophthalmological surgery within the previous 6 months, had another uncontrolled illness, or who were pregnant or lactating, were excluded from the study. Postmenopausal women receiving hormonal replacement therapy were also excluded.

**Baseline comparison**: no significant differences in the baseline demographic and ocular characteristics were observed between the FML and the CsA groups (Table 1)

| | |
|---|---|
| Interventions | • **Fluorometholone (FML) 0.1% plus hyaluronic acid (HA) 0.1%**, FML/HA 4 times a day for 8 weeks<br>• **Cyclosporine A (CsA) 0.5% plus hyaluronic acid (HA) 0.1%**, CsA 2 times/HA 4 times a day for 8 weeks |
| Outcomes | **Time points of primary outcome data collected**: week 2, 4, and 8 after the first treatment<br><br>**Primary outcomes of the study**:<br><br>1. TBUT<br>2. Schirmer test I without anesthesia<br>3. Corneal fluorescein staining<br><br>**Other outcomes of the study**:<br><br>1. OSDI symptom scores<br>2. Conjunctival congestion evaluation<br>3. Cytological examination<br>4. Visual acuity<br>5. IOP |

**Lin 2015** *(Continued)*

| | |
|---|---|
| Study Identification | **Sponsorship source:** the authors have no funding and conflicts of interest to disclose<br><br>**Ethics approval:** "Our study was conducted in compliance with the Declaration of Helsinki for research involving human participants and was approved by the Ethics Committee of the EENT Hospital of Fudan University"<br><br>**Correspondence author's name:** Lan Gong; Institution: Department of Ophthalmology, Eye, Ear, Nose, and Throat Hospital of Fudan University, Shanghai, China<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: the authors have no funding and conflicts of interest to disclose |
| Notes | |

**Luo 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2011/01<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2011/06<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR<br><br>**05. Study visits and the corresponding time points**: baseline (before) and 1 week after treatment (after)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: dryness symptom questionnaire for dryness, foreign body sensation, burning, fatigue, photophobia, and stinging; the scale (0 to 5), 0 for no symptom, 1 for occasional symptom (< 3 times/week occurrence and relieved with rest), 2 for frequent occurrences (≥ 3 times/week), 3 for frequent symptoms affecting daily life (≥ 6 times/week, not relieved by rest), 4 for ≥ 10 times/week and not relieved by medications, 5 for persistent symptoms that severely affected daily life<br><br>**07. Assessment for safety outcomes**: NR<br><br>**08. Planned follow-up duration**: 1 week<br><br>**09. Actual follow-up duration**: 1 week<br><br>**10. Planned treatment duration (of the intervention steroid)**: 1 week<br><br>**11. How missing data were handled**: NA<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country**: China<br><br>**Setting**: single medical center<br><br>**Intervention**:<br><br>• **Dexamethasone plus tobramycin 3 g/L** |

**Luo 2013** *(Continued)*

| | |
|---|---|
| | Age, mean/SD (range): NR<br>Female, n (%): NR<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 15<br>Participants (eyes) analyzed for primary study outcomes: 15<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>• **Artificial tears plus tobramycin 3 g/L**<br><br>Age, mean/SD (range): NR<br>Female, n (%): NR<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 15<br>Participants (eyes) analyzed for primary study outcomes: 15<br>Participants (eyes) analyzed for safety outcomes: 15<br><br>• **Overall**<br><br>Age, mean/SD (range): 35.6/6.7 (18 to 72), including participants in the tobramycin-alone group<br>Female, n (%): 27 (60%), including participants in the tobramycin-alone group<br>Etiology, n (%): MGD (100%)<br>Participants (eyes) randomized: 30<br>Participants (eyes) analyzed for primary study outcomes: 30<br>Participants (eyes) analyzed for safety outcomes: NR<br><br>Note: data were not shown for a third group treated with tobramycin 3 g/L with local physical therapy (N = 15).<br><br>**Inclusion criteria**: patients with MGD, which was diagnosed based on symptoms, slit lamp exam, and instability of the tear film<br><br>**Exclusion criteria**: NR<br><br>**Baseline comparison**: there were no statistical differences in baseline characteristics (age or sex), symptoms, and clinical signs among the 3 groups (Table 1) |
| Interventions | • **Dexamethasone plus tobramycin 3 g/L**, 4 times a day for 1 week<br>• **Aritficial tears plus tobramycin 3 g/L**, 4 times a day for 1 week |
| Outcomes | **Time points of primary outcome data collected**: week 1<br><br>**Primary outcomes of the study**: symptom; TBUT; Schirmer's I test; corneal fluorescein staining (lid margin) score<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source:** NR<br><br>**Ethics approval**: NR<br><br>**Correspondence author's name**: Cheng Lei; Institution: Department of Ophthalmology, General Hospital of Wuhan Steel and Iron Group Corp, Wuhan Hubei, China<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

**NCT01276223**

| *Study characteristics* | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2011/02 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2012/01 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double (participant, investigator)<br><br>**05. Study visits and the corresponding time points**: baseline, week 1, 2, 3, 4<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: VAS was used by the participant to assess ocular discomfort, both frequency and severity, at baseline (pre-treatment) and weekly thereafter for 4 additional weeks. Each scale was 100 mm in length. The VAS score was calculated by measuring the length in millimeters from the start of the line to the intersection point of the vertical mark made by the participant. The Global Ocular Discomfort Score is a composite of the 2 VAS scores, ranging from 0 (very mildly) to 100 (very severely uncomfortable).<br><br>**07. Assessment for safety outcomes**: NR<br><br>**08. Planned follow-up duration**: 4 weeks<br><br>**09. Actual follow-up duration**: 4 weeks<br><br>**10. Planned treatment duration (of the intervention steroid)**: 4 weeks<br><br>**11. How missing data were handled**: of the 722 participants enrolled, 433 did not qualify for run-in and were exited without exposure to product. Of the 289 participants entering run-in, 78 did not qualify for treatment. The 211 participants qualifying for treatment were randomized 1:1 to receive either difluprednate (Durezol) or vehicle. Mixed model repeated measure (MMRM) approach was used to handle missing data during the randomized treatment period; 4 and 3 participants in the difluprednate and vehicle groups did not complete the study.<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country**: USA<br><br>**Setting**: participants were recruited from 25 investigative sites<br><br>**Interventions:**<br><br>• **Difluprednate 0.05% ophthalmic emulsion (Durezol)**<br><br>Age, mean/SD (range): 54.4/14.8<br>Female, n (%): 90 (84.1%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 107<br>Participants (eyes) analyzed for primary study outcomes: 107<br>Participants (eyes) analyzed for safety outcomes: 107<br><br>• **Difluprednate vehicle**<br><br>Age, mean/SD (range): 60.1/13.8<br>Female, n (%): 85 (81.7%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 104<br>Participants (eyes) analyzed for primary study outcomes: 104<br>Participants (eyes) analyzed for safety outcomes: 104 |

**NCT01276223** *(Continued)*

- **Overall**

Age, mean/SD (range): 57.2/14.6
Female, n (%): 175 (82.9%)
Etiology, n (%): NR
Participants (eyes) randomized: 211
Participants (eyes) analyzed for primary study outcomes: 211
Participants (eyes) analyzed for safety outcomes: 211

**Inclusion criteria**:

1. Normal subjects: no known history of dry eye disease; non-contact lens wearer; no current use of artificial tears or any other dry eye treatment
2. Dry eye patients: at least a 6-month history of dry eye; non-contact lens wearer; uses artificial tears; experiences persistent ocular discomfort; other protocol-defined inclusion criteria may apply

**Exclusion criteria**:

1. The presence of any acute infectious or non-infectious ocular conditions in either eye within 1 month of visit 1
2. Severe Sjögren's syndrome
3. Lid function abnormalities
4. Use of steroids, tetracycline, doxycycline, etc., within 30 days of visit 1
5. History of corneal surgery including refractive surgeries
6. History of glaucoma or ocular hypertension
7. Other protocol-defined exclusion criteria may apply

**Baseline comparison**: participants in the difluprednate group were 5.7 years younger than those in the vehicle group (post hoc P = 0.004)

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|---|---|
| Interventions | • **Difluprednate 0.05% ophthalmic emulsion (Durezol)**, 1 drop to the study eye 2 times a day for 4 weeks, followed by 1 drop to the study eye once daily for 1 week to allow for tapering<br>• **Difluprednate vehicle**, 1 drop to the study eye 2 times a day for 4 weeks, followed by 1 drop to the study eye once daily for 1 week |
| Outcomes | **Time points of primary outcome data collected**: at week 4<br><br>**Primary outcomes of the study**: mean change from baseline (Week 0) in VAS Global Ocular Discomfort Score over 4 weeks<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source**: Alcon Research<br><br>**Ethics approval**: NR<br><br>**Correspondence author's name**: NR<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT01276223<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: NR |
| Notes | |

## Pflugfelder 2004

***Study characteristics***

| | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): NR<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: "Eligible patients received a study number and received double-masked study medication (either loteprednol or placebo) according to a predetermined random allocation schedule"<br><br>**05. Study visits and the corresponding time points**: Visit 1 (day −14 to −7), Visit 2 (day 1 or baseline), Visit 3 (day 14 ± 3), Visit 4 (day 28 ± 3), Visit 5 (day 42 ± 3)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: "A VAS score for the worst symptom at visit 2 was chosen as the subjective variable. The patients were asked to grade the severity of the following symptoms: burning/stinging, itching, grittiness/scratchiness/foreign body sensation, dryness, stickiness, redness of the eye, and tired eye sensation. Symptoms were graded for each eye separately and for the conditions upon waking and during the day. The VAS—a 100-mm line, marked at the left end“Absent” and at the right end “Unbearable”—was provided for this purpose. The patient was asked to mark the line at the point between these two extremes that represented the severity of the symptom; the distance from the left end of the line to the mark was the VAS score in millimeters."<br><br>**07. Assessment for safety outcomes**: "Safety was assessed by funduscopy, lens examination and biomicroscopy, tests of visual acuity and intraocular pressure, and monitoring adverse events and changes in symptoms. Adverse events were evaluated by the investigator as to severity (mild, moderate, severe) and relationship of the event to the study drug (probable, possible, unlikely, or unknown)."<br><br>**08. Planned follow-up duration**: 42 ± 3 days<br><br>**09. Actual follow-up duration**: 42 ± 3 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 28 ± 3 days<br><br>**11. How missing data were handled**: NR<br><br>**12. Description on power and sample size calculation**: "Since this was a pilot study, the calculation of the sample size was based on the best available relevant publications. ... Thus, the planned sample size of 30 per group was expected to provide adequate sensitivity to differentiate between the loteprednol and the placebo groups with respect to both the subjective and objective outcome parameters" |
| Participants | **Country**: USA<br><br>**Setting**: multicenter pilot study<br><br>**Interventions**:<br><br>• **Loteprednol etabonate (LE) ophthalmic suspension, 0.5%**<br><br>Age, mean/SD (range): 57.6<br>Female, n (%): 20 (63%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 32<br>Participants (eyes) analyzed for primary study outcomes: 32<br>Participants (eyes) analyzed for safety outcomes: 32<br><br>• **Placebo**<br><br>Age, mean/SD (range): 56.2 |

**Pflugfelder 2004** *(Continued)*

Female, n (%): 30 (88%)
Etiology, n (%): NR
Participants (eyes) randomized: 34
Participants (eyes) analyzed for primary study outcomes: 34
Participants (eyes) analyzed for safety outcomes: 34

- **Overall**

Age, mean/SD (range): 56.9
Female, n (%): 50 (76%)
Etiology, n (%): NR
Participants (eyes) randomized: 66
Participants (eyes) analyzed for primary study outcomes: 66
Participants (eyes) analyzed for safety outcomes: 66

**Inclusion criteria**:

1. Eligible patients were age 18 years or older with a diagnosis of keratoconjunctivitis sicca of at least 6 months' duration
2. They were required to meet the following criteria in at least 1 eye:
   a. delayed tear clearance defined by a standardized visual scale score of ≥ 3;
   b. at least 1 symptom > 30 mm on VAS; and
   c. composite corneal staining score of ≥ 3.

**Exclusion criteria**:
Female patients were either postmenopausal or using a recognized, reliable method of contraception; pregnant or lactating females; patients with contraindications to the use of topical corticosteroid eye drops or their components; patients with illnesses that could interfere with the study; ocular infections or a history of herpes simplex infection were also excluded. Further exclusions were made for contact lens use, punctal occlusion within 3 months, systemic corticosteroid use in the last 6 months, topical corticosteroid use in the last 2 months, and concurrent use of ophthalmic medications for conditions other than keratoconjunctivitis sicca. Ophthalmic surgery in the past 6 months, participation in another clinical study, or use of experimental medication in the past 30 days also disqualified patients from participation.

**Baseline comparison**: the majority of participants were female (75.7%), and there was a slightly larger preponderance of female participants in the vehicle-treated group (88.2%) vs the loteprednol-treated group (62.5%) (Table 3)

| | |
|---|---|
| Interventions | • **Loteprednol etabonate (LE) ophthalmic suspension 0.5%**, 4 times a day for 28 days<br>• **Placebo**, 4 times a day for 28 days |
| Outcomes | **Time points of primary outcome data collected**: 28 ± 3 days<br><br>**Primary outcomes of the study**: changes in the following 2 variables at week 4 from baseline:<br><br>1. Primary objective variable: the combined corneal staining score, which was the sum of the scores for the 5 areas of the cornea (central, inferior, nasal, superior, and temporal);<br>2. Primary subjective variable: a VAS for the worst symptom in the worst eye.<br><br>**Other outcomes of the study**: secondary analyses included the following, calculated as a change from Visit 2 to Visits 4 and 5, respectively:<br><br>1. All symptom VAS scores;<br>2. Amount of preservative-free lubricant eye drops used;<br>3. Schirmer 1 test scores;<br>4. Fluorescein staining scores for the 5 areas of the cornea;<br>5. Biomicroscopic findings (lid margin and conjunctival injection, filamentary keratitis). |
| Study Identification | **Sponsorship source**: Bausch & Lomb, Rochester, NY, USA |

**Pflugfelder 2004** *(Continued)*

**Ethics approval**: approval was obtained from an IRB for each study site before the study was initiated

**Correspondence author's name:** Stephen P Bartels; Institution: Bausch & Lomb

**Additional information:**

1. Trial registration no.: NR
2. Trial registration website: NR
3. Financial disclosure or conflicts of interest statement from authors: SPB and TM were employers of Bausch & Lomb, Rochester, NY, USA

| | |
|---|---|
| Notes | 92.4% of the participants were white. |

**Pinto-Fraga 2016**

***Study characteristics***

| | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2014/03 (ClinicalTrials.gov: 2014/02)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2014/11 (ClinicalTrials.gov: 2014/12)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: participants, treatment allocators, and outcome assessors (examiners)<br><br>**05. Study visits and the corresponding time points**: Day 0 (Visit 1), Day 21 (Visit 2 and Visit 3), Day 22 (Visit 4)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI, SANDE version I<br><br>**07. Assessment for safety outcomes**: the safety of both treatments was assessed by recording the nature, severity, and duration of all adverse events and their relationship to the study medication. 4 additional safety endpoints were included in the trial (Table 1): changes in BCVA, fundus evaluation and optic cup-to-disc ratio, anterior segment anomalies (especially corneal epithelial problems or signs of infection), and IOP.<br><br>**08. Planned follow-up duration**: 22 days<br><br>**09. Actual follow-up duration**: 22 days<br><br>**10. Planned treatment duration (of the intervention steroid)**: 21 days<br><br>**11. How missing data were handled**: "because 1 patient dropped from the study because of work-related issues, 1 more individual was recruited, and thus a total of 41 patients eventually were included in the study, but data from only 40 patients were analyzed"<br><br>**12. Description on power and sample size calculation**: the sample size was estimated to detect a 1-point difference (Oxford scale) in the main efficacy variable (corneal fluorescein staining), at a significance level of 0.05, with a statistical power of 0.9, and with an estimate of a 10% loss of the sample size |
| Participants | **Country:** Spain<br><br>**Setting:** single medical center<br><br>**Interventions:** |

**Pinto-Fraga 2016** *(Continued)*

- **Fluorometholone (FML) 0.1%, 4 times a day for 21 days**

Age, mean (95% CI): 59.0 (55.2 to 62.7)
Female, n (%): 17 (81%)
Etiology, n (%): NR
Participants (eyes) randomized: 21
Participants (eyes) analyzed for primary study outcomes: 21
Participants (eyes) analyzed for safety outcomes: 21

- **Liquifilm artificial tears eyedrops, 4 times a day for 21 days**

Age, mean (95% CI): 60.3 (56.0 to 64.7)
Female, n (%): 17 (89%)
Etiology, n (%): NR
Participants (eyes) randomized: 19
Participants (eyes) analyzed for primary study outcomes: 19
Participants (eyes) analyzed for safety outcomes: 19

- **Overall**

Age, mean (95% CI): 59.6 (58.9 to 60.3)
Female, n (%): 34 (85%)
Etiology, n (%): NR
Participants (eyes) randomized: 40
Participants (eyes) analyzed for primary study outcomes: 40
Participants (eyes) analyzed for safety outcomes: 40

**Inclusion criteria**:
Corneal fluorescein staining score of 1 or more (Oxford scale) in both eyes, a TBUT of 7 seconds or less in both eyes, unanesthetized Schirmer test results of 10 mm/5 min or less in both eyes, and an OSDI score of 12 points or more. Importantly, the patient had to express a worsening of DED-related symptoms when exposed to adverse environmental conditions during their daily life and the use of artificial tears before beginning the study. Patients were accepted into the study if they were taking other topical or systemic treatment if it was begun at least 3 months before inclusion, and the dosage was to be maintained throughout the entire study. Finally, patients had to have a BCVA of 1.0 logarithm of the minimum angle of resolution or less in each eye.

**Exclusion criteria**:
Patients were excluded if they had a known sensitivity or intolerance to any of the treatments used in the study; a history of ocular infection or severe ocular inflammation (other than DED related) 6 months before inclusion in the study; any active ocular disease (different from DED); any uncontrolled severe systemic disease that may affect the eye (except Sjögren syndrome); any ocular surgery or trauma that could affect corneal sensitivity, normal tear distribution in the 6 previous months, any ocular or systemic surgery or procedure planned during the study duration that could affect outcomes, or a combination thereof; occlusion of the lacrimal puncta either surgically or with plugs within 3 months before study; contact lenses wear within 3 months or during the study; or use of any topical medication except for DED. Other exclusion criteria included initiation, discontinuation, or change of dosage of antihistaminic, cholinergic agents, beta-blocking agents, antidepressants, or any systemic medication with possible effects over the tear film; history of glaucoma or IOP of more than 22 mmHg in any measurements 2 months before baseline; optic cup-to-disc ratio of more than 0.6 mm; pregnancy; lactation; or inadequate contraception. Also, patients were excluded if undergoing topical cyclosporine A eye drops within 3 months before study inclusion, topical corticosteroid eye drops within 1 month before inclusion, or both.

**Baseline comparison**: for baseline clinical characteristics, there were no statistical differences (P = 0.06) between groups in corneal and conjunctival staining, hyperemia, TBUT, unanesthetized Schirmer test results, BCVA, tear osmolarity, or IOP (Table 4)

| | |
|---|---|
| Interventions | • **Fluorometholone (FML) 0.1%**, 4 times a day for 21 days<br>• **Liquifilm artificial tears eyedrops**, 4 times a day for 21 days |

**Pinto-Fraga 2016** *(Continued)*

| | |
|---|---|
| Outcomes | **Time points of primary outcome data collected**: between Visits 2 and 3, i.e. before and after 2 hours of desiccating stress in participants treated for 21 days<br><br>**Primary outcomes of the study**:<br><br>1. Efficacy outcomes were evaluated as changes in corneal fluorescein staining and symptoms<br>2. For fluorescein staining, the change was recorded in the percentage of participants with an increase of 1 point or more in corneal staining between Visits 2 and 3, i.e. before and after 2 hours of desiccating stress in participants treated for 21 days. Staining was measured again after Visit 4 on day 22 to determine the recovery from 2 hours of desiccating stress during Visit 3<br>3. For symptoms, the change was recorded in the percentage of participants with a reduction of 2 points or more in SANDE score between Visits 2 and 3 and again between Visits 3 and 4<br><br>**Other outcomes of the study**:<br>All other evaluations were considered as secondary variables measuring efficacy, except those included as safety measures (Table 1); these included OSDI scores, BCVA (high and low contrast), tear osmolarity, treatment satisfaction, TBUT, Lissamine green conjunctival staining, biomicroscopy with slit lamp, Schirmer test (unanesthetized), IOP, fundus evaluation, and optic cup-to-disc ratio. These were evaluated between Visits 1 and 2, 2 and 3, and 3 and 4. |
| Study Identification | **Sponsorship source**: the study was sponsored by and conducted at Instituto Universitario de Oftalmobiología Aplicada, University of Valladolid, Valladolid, Spain (in the text). According to the footnotes of the article, the study was supported by the Spanish Ministry of Economy and Competitiveness (grant no.: SAF2010-15361); European Social Funds, Operative Program for Castilla y León, Castilla y León Council, Spain (grant no.: EDU/346/2013); and the Inflammation Research Program, Allergan Inc (Irvine, CA, USA) (contributed extra funding for environmental chamber use).<br><br>**Ethics approval**: "This clinical trial was approved by the University Hospital Ethics Committee (Valladolid, Spain) and by the Spanish Regulatory Agency (Spanish Drugs and Health Products Administration; www.aemps.gob.es/en/home.htm) with EUDRA (European Union Drug Regulating Authorities) number 2013-002183-63"<br><br>**Correspondence author's name:** Margarita Calonge, MD, PhD; Institution: Instituto Universitario de Oftalmobiología Aplicada, Universidad de Valladolid<br><br>**Additional information:**<br><br>1. Trial registration no.: NCT02051023<br>2. Trial registration website: ClinicalTrials.gov<br>3. Financial disclosure or conflicts of interest statement from authors: MC: Consultant, Allergan, Inc (Irvine, CA, USA); financial support, Abbott (Chicago, IL, USA); Novartis (Basel, Switzerland); Alcon (Ontario, Canada); Xoma (Berkeley, CA, USA); Servier (Suresnes, France); Allergan-Spain Laboratories (Madrid, Spain). MES: Employee e Allergan Inc (Irvine, CA, USA). AL-M: Employee e VISIÓN IþD, SL (Valladolid, Spain) |
| Notes | |

**Qazi 2015**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2011/08 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2013/03; 2017/06 (ClinicalTrials.gov) |

**Qazi 2015** *(Continued)*

**03. Unit of randomization (participant or eye)**: participant

**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: quadruple (participant, care provider, investigator, outcomes assessor)

**05. Study visits and the corresponding time points**: baseline, week 4 (after treatment), week 8 (4 weeks after treatment cessation)

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI; SANDE
1. OSDI: a 12-question survey used to measure the symptoms of dry eye disease
2. SANDE: the range of the SANDE frequency scale is 0 to 100, with 0 being the minimum level of frequency of dry eye symptoms, and 100 being the maximum level of frequency of dry eye symptoms; the range of the SANDE severity scale is 0 to 100, with 0 being the minimum level of severity of dry eye symptoms, and 100 being the maximum level of severity of dry eye symptoms

**07. Assessment for safety outcomes**: NR

**08. Planned follow-up duration**: 8 weeks

**09. Actual follow-up duration**: 8 weeks

**10. Planned treatment duration (of the intervention steroid)**: 4 weeks

**11. How missing data were handled**: complete-case analysis for outcome data

**12. Description on power and sample size calculation**: NR

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Participants

**Country:** USA

**Setting:** single-site

**Interventions**

- **Loteprednol etabonate (LE) 0.5% (Lotemax)**

Age, mean/SD (range): 52/12
Female, n (%): 9 (45%)
Etiology, n (%): NR
Participants (eyes) randomized: 20
Participants (eyes) analyzed for primary study outcomes: 17
Participants (eyes) analyzed for safety outcomes: 20

- **Loteprednol etabonate (LE) 0.5% plus tobramycin (Zylet)**

Age, mean/SD (range): 55/13
Female, n (%): 8 (47%)
Etiology, n (%): NR
Participants (eyes) randomized: 20
Participants (eyes) analyzed for primary study outcomes: 17
Participants (eyes) analyzed for safety outcomes: 20

- **Artificial tears (AT)**

Age, mean/SD (range): 57/12
Female, n (%): 15 (30%)
Etiology, n (%): NR
Participants (eyes) randomized: 20
Participants (eyes) analyzed for primary study outcomes: 20
Participants (eyes) analyzed for safety outcomes: 20

- **Overall**

Age, mean/SD (range): 55/12
Female, n (%): 24 (53%)

**Qazi 2015** *(Continued)*

Etiology, n (%): MGD 54 (100%)
Participants (eyes) randomized: 60
Participants (eyes) analyzed for primary study outcomes: 54
Participants (eyes) analyzed for safety outcomes: 60

**Inclusion criteria**:

1. Male or female
2. At least 18 years of age and has not worn contact lenses, except for bandage contact lens or rigid gas permeable lens, for at least 2 weeks prior to the study and agrees to not wear contact lenses during study
3. Patient is in generally good and stable overall health
4. Minimum corneal fluorescein staining of 4 in at least 1 eye
5. OSDI score > 22
6. The patient must have a diagnosis of posterior blepharitis (or MGD)
7. A negative urine pregnancy test result for women of childbearing potential
8. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation
9. Normal lid position and closure
10. Ability to understand and provide informed consent to participate in this study
11. Willingness to follow study instructions and likely to complete all required visits

**Exclusion criteria**:

1. History of Stevens-Johnson syndrome or ocular pemphigoid
2. History of eyelid surgery
3. Intraocular surgery or ocular laser surgery within 3 months
4. History of microbial keratitis, including herpes
5. Active ocular allergies
6. Corneal epithelial defect > 1 $mm^2$
7. Any change in use of topical anti-inflammatories, such as steroids, ciclosporin (Restasis), or NSAID within the past 2 weeks
8. Any change in dosage of tetracycline compounds (tetracycline, doxycycline, and minocycline) within the past 2 weeks
9. Use of isotretinoin (Accutane) within the past 6 months
10. Pregnant or lactating women
11. Signs of current infection, including fever and current treatment with antibiotics
12. Active liver, renal, or hematologic disease
13. The use of any other investigational drug
14. Individuals with a known history of glaucoma, individuals with IOP > 22 mmHg in either eye, and individuals with a known family history of glaucoma in primary (first-degree) relatives (i.e. mother, father, sibling, or child)

**Baseline comparison**: no significant differences in baseline characteristics of participants among the 3 comparison groups (ClinicalTrials.gov)

| | |
|---|---|
| Interventions | • **Loteprednol etabonate (LE) 0.5%**, 2 times a day for 4 weeks<br>• **Artificial tears**, 2 times a day for 4 weeks |
| Outcomes | **Time points of primary outcome data collected**: 4 weeks<br><br>**Primary outcomes of the study**:<br><br>1. OSDI<br>2. SANDE frequency score<br>3. SANDE severity score<br>4. Corneal fluorescein stain score (NEI scale, 0 to 15) |

**Qazi 2015** *(Continued)*

**Other outcomes of the study**:

1. BCVA
2. IOP
3. Conjunctival staining with Lissamine green (NEI scale, 0 to 18)
4. TBUT
5. Schirmer's test with anesthesia
6. Corneal subbasal nerve fiber length via in vivo confocal microscopy

| | |
|---|---|
| Study Identification | **Sponsorship source**: Massachusetts Eye and Ear Infirmary (MEEI); Bausch & Lomb Inc (conference abstract); Bausch & Lomb Inc, National Institutes of Health K24- EY019098, Falk Medical Research Trust (full publication)<br><br>**Ethics approval**: "The study protocol was approved by the Human Studies Committee of the Massachusetts Eye and Ear Infirmary (Boston, MA), and the research was conducted in accord with the requirements of the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki."<br><br>**Correspondence author's name**: Reza Dana; Institution: Massachusetts Eye and Ear Infirmary<br><br>**Additional information:**<br>**01. Trial registration no.**: NCT01456780<br>**02. Trial registration website**: ClinicalTrials.gov<br>**03. Financial disclosure or conflicts of interest statement from authors**:<br>Conference abstract: Yureeda Qazi, none; Ahmad Kheirkhah, none; Thomas Dohlman, none; Andrea Cruzat, none; Bernardo Cavalcanti, none; Clara Colon, none; Reza Dana, Bausch & Lomb (F), MEEI (P); Pedram Hamrah, MEEI (P)<br>Full-text publication: RD, personal fees: Eleven Biotherapeutics, Alcon Laboratories Inc, Allergan Inc, Bausch & Lomb Inc, Genentech, outside the submitted work, and has a US Patent Application pending |
| Notes | From the full-text publication: "This study was partly presented at: the Annual Meeting of the Association for Research in Vision and Ophthalmology, May 4e8, 2014, Orlando, Florida. This manuscript is not an Annual Meeting paper or poster" |

**Sheppard 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2006/11 (ClinicalTrials.gov)<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): 2007/09 (ClinicalTrials.gov)<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: double (participant, investigator)<br><br>**05. Study visits and the corresponding time points**: study visits occurred on day 1 (screening and baseline, Visit 1), 14 ± 2 days (Visit 2), 30 ± 3 days (Visit 3), and 60 ± 5 days (Visit 4)<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI: a global assessment of their perceptions about their dry eye condition and how it had impacted their vision and daily activities at Visits 2, 3, and 4 and also rated the tolerability of the topical CsA drops since the previous study visit at the third and fourth study visits |

**Sheppard 2014** *(Continued)*

**07. Assessment for safety outcomes**: safety outcomes included ocular and systemic adverse events, IOP, and ophthalmoscopic examination findings

**08. Planned follow-up duration**: 60 days

**09. Actual follow-up duration**: 60 ± 5 days

**10. Planned treatment duration (of the intervention steroid)**: 60 days

**11. How missing data were handled**: complete-case analysis

**12. Description on power and sample size calculation**: the calculations were based on a power of 80% with an alpha of 0.05 (2-tailed) and also used published data to estimate standard deviations for individual parameters of the study, which included OSDI, Lissamine staining (NEI scale), central fluorescein staining (NEI scale), and Schirmer test

| | |
|---|---|
| Participants | **Country**: USA<br><br>**Setting**: multicenter<br><br>**Interventions**:<br><br>• **Loteprednol etabonate (LE) 0.5% plus cyclosporine A 0.05% (CsA, Restasis)**<br><br>Age, mean/SD (range): 59.6/12.1 (27 to 80)<br>Female, n (%): 44 (77%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: NR<br>Participants (eyes) analyzed for primary study outcomes: 57<br>Participants (eyes) analyzed for safety outcomes: 57<br><br>• **Artificial tears (AT) plus cyclosporine A 0.05% (CsA, Restasis)**<br><br>Age, mean/SD (range): 57.9/1038 (36 to 79)<br>Female, n (%): 43 (78%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: NR<br>Participants (eyes) analyzed for primary study outcomes: 55<br>Participants (eyes) analyzed for safety outcomes: 55<br><br>• **Overall**<br><br>Age, mean/SD (range): 58.7/11.4 (24 to 80)<br>Female, n (%): 87 (78%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 116<br>Participants (eyes) analyzed for primary study outcomes: 112<br>Participants (eyes) analyzed for safety outcomes: 112<br><br>**Inclusion criteria**:<br><br>1. Between 30 and 80 years of age<br>2. Has not worn contact lenses for at least 1 month before the study and agrees to not wear contact lenses during the study<br>3. Oral medications stable 1 month before study<br>4. Oral medications anticipated to be stable during 60 days study<br>5. Patient is in generally good and stable overall health<br>6. Corneal stain, conjunctival stain, OSDI, or using regular AT at least on average twice a day<br>7. Informed consent signed<br><br>**Exclusion criteria**:<br><br>1. History of Stevens–Johnson syndrome or ocular pemphigoid |

**Sheppard 2014** *(Continued)*

2. Punctal plugs inserted or punctual cautery in the past 3 month
3. Intraocular surgery within 3 months
4. History of liver disease
5. Pregnant or lactating women
6. Severe clinical vitamin deficiencies or history of vitamin overdose
7. Highly variable vitamin intake
8. Unstable use of systemic or topical medications known to create dry eye
9. Corneal pathology that could cause an ocular surface disorder
10. Use of glaucoma medications, topical or oral
11. Unstable diabetes mellitus
12. Allergy or sensitivity to Lotemax, Restasis, or the OTC tear supplement
13. Use of topical steroids or Restasis within the past 1 month
14. Use of other topical ocular agents other than tear replacements within the past 1 week

**Baseline comparison**: there were no statistically significant differences in baseline characteristics within and between treatment groups (Table 2)

Interventions

- **Loteprednol etabonate (LE) plus cyclosporine A 0.05% (CsA, Restasis)**, LE 4 times daily for 2 weeks, then CsA 2 times a day was added for day 15 to day 60
  - LE run-in for 2 weeks before adding CsA
- **Artificial tears (AT) plus cyclosporine A 0.05% (CsA, Restasis)**, AT 4 times daily for 2 weeks, then CsA 2 times a day was added for day 15 to day 60

Outcomes

**Time points of primary outcome data collected**: day 14, 30, and 60

**Primary outcomes of the study**:
The primary efficacy outcomes included:

1. a 12-item OSDI questionnaire;
2. Likert scale using standardized facial expressions;
3. Lissamine green staining (NEI scale);
4. fluorescein staining (NEI scale);
5. Schirmer tear test.

**Other outcomes of the study**: frequency of adjunctive tear use (> 6/d, 3 to 6/d, 1 to 2/d, none)

Study Identification

**Sponsorship source**: Supported by an unrestricted research grant from Bausch & Lomb Inc, Rochester, NY, USA, and the Virginia Eye Foundation, Norfolk, VA, USA

**Ethics approval**: NR

**Correspondence author's name**: John D Sheppard; Institution: Virginia Eye Consultants, Norfolk, VA, USA

**Additional information:**

1. Trial registration no.: NCT00407043
2. Trial registration website: ClinicalTrials.gov
3. Financial disclosure or conflicts of interest statement from authors: the authors have no other conflicts of interest or funding to declare

Notes

- 77% of the study participants were white

**Sheppard 2014** *(Continued)*

- Presented at the American Academy of Ophthalmology Annual Meeting, New Orleans, LA, November 2007; the Royal Hawaiian Eye Meeting, Wailea, Hawaii, January 2008; and the Association for Research in Vision and Ophthalmology Meeting, Ft Lauderdale, FL, April 2008

**Singla 2019**

| *Study characteristics* | |
|---|---|
| Methods | **00. Study design:** randomized controlled trial, parallel group<br><br>**01. Calendar time when the study enrolled the first participant** (YYYY/MM): NR<br><br>**02. Calendar time when the study completed follow-up** (YYYY/MM): NR<br><br>**03. Unit of randomization (participant or eye)**: participant<br><br>**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR<br><br>**05. Study visits and the corresponding time points**: baseline, 2 weeks, 6 weeks, 3 months, and 6 months<br><br>**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: OSDI questionnaire was used for grading the severity of dry eye. This questionnaire consists of 12 questions and is graded on a scale from 0 to 100. OSDI score of 16 to 30 was included for the diagnosis of moderate dry eye disease.<br><br>**07. Assessment for safety outcomes**: IOP<br><br>**08. Planned follow-up duration**: 6 months<br><br>**09. Actual follow-up duration**: 6 months<br><br>**10. Planned treatment duration (of the intervention steroid)**: 3 months<br><br>**11. How missing data were handled**: NA<br><br>**12. Description on power and sample size calculation**: NR |
| Participants | **Country:** India<br><br>**Setting:** single-site<br><br>**Interventions**<br><br>• **Loteprednol 0.5% plus cyclosporine A (CsA) 0.05% plus artificial tears (AT)**<br><br>Age, mean (range): 44.4 (25 to 68)<br>Female, n (%): 45 (64%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 70<br>Participants (eyes) analyzed for primary study outcomes: 70<br>Participants (eyes) analyzed for safety outcomes: 70<br><br>• **CsA 0.05% plus AT**<br><br>Age, mean (range): 44.6 (23 to 69)<br>Female, n (%): 45 (64%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 70<br>Participants (eyes) analyzed for primary study outcomes: 70 |

**Singla 2019** *(Continued)*

| | |
|---|---|
| | Participants (eyes) analyzed for safety outcomes: 70<br><br>• **Overall**<br><br>Age, mean/SE (range): 44.5/7.7 (23 to 69)<br>Female, n (%): 90 (64.3%)<br>Etiology, n (%): NR<br>Participants (eyes) randomized: 140<br>Participants (eyes) analyzed for primary study outcomes: 140<br>Participants (eyes) analyzed for safety outcomes: 140<br><br>**Inclusion criteria**:<br>Patients above 18 years of age, diagnosed with moderate dry eye, who were not wearing contact lenses for at least 1 month before the study and agree not to wear the same during the study period were included in the study<br><br>**Exclusion criteria**:<br><br>1. History of Stevens-Johnson syndrome or ocular pemphigoid<br>2. Those having punctual plugs or cautery or any intraocular surgery in the past 3 months<br>3. Pregnant or lactating women or those on oral contraceptive pills<br>4. Patients on antiglaucoma medications<br>5. Patients with unstable diabetes mellitus<br>6. Patients allergic to study medications<br>7. Patients having a history of topical steroid or ciclosporin use within 1 month<br>8. Patients who could not complete 6 months of follow-up<br><br>**Baseline comparison**: both groups had comparable baseline parameters, and there was no statistically significant difference between groups in terms of OSDI scores, TBUT values, Schirmer's test values, corneal fluorescein staining scores, and Lissamine green conjunctival staining scores, which may suggest *excessive balance* between the two groups |
| Interventions | • **Loteprednol 0.5% plus cyclosporine A (CsA) 0.05% plus artificial tears (AT)**, topical loteprednol 0.5% was given for 8 weeks, started as 4 times per day for the first 2 weeks and tapered to 2 times per day dosage for 3rd to 8th week, and topical CsA 0.05% was given twice a day for 3 months<br>  ○ Loteprednol run-in concurrently with CsA<br>• **CsA 0.05% plus AT**, topical CsA 0.05% was given twice a day for 3 months |
| Outcomes | **Time points of primary outcome data collected**: 2 weeks, 6 weeks, 3 months, and 6 months<br><br>**Primary outcomes of the study**:<br><br>1. OSDI symptom scores<br>2. TBUT test scores<br>3. Schirmer's test<br>4. Corneal fluorescein staining<br>5. Lissamine green staining<br><br>**Other outcomes of the study**: NR |
| Study Identification | **Sponsorship source**: NR<br><br>**Ethics approval**: approval of the Institute's Ethics Committee was obtained before starting the study<br><br>**Correspondence author's name**: Mukesh Joshi; Institution: Safdarjung Hospital, New Delhi, India<br><br>**Additional information:**<br><br>1. Trial registration no.: NR<br>2. Trial registration website: NR |

**Singla 2019** *(Continued)*

3. Financial disclosure or conflicts of interest statement from authors: the authors declare that there are no conflicts of interests of this paper

Notes

**Wan 2012**

***Study characteristics***

Methods

**00. Study design:** randomized controlled trial, parallel group

**01. Calendar time when the study enrolled the first participant** (YYYY/MM): 2009/03

**02. Calendar time when the study completed follow-up** (YYYY/MM): 2010/09

**03. Unit of randomization (participant or eye)**: participant

**04. Masking of participants, treatment allocator, outcome assessor, or data analyzer**: NR

**05. Study visits and the corresponding time points**: baseline, weeks 2, 4, 6, 8

**06. Instruments and the scales used for documenting patient-reported symptoms or quality of life**: symptom scale (0 to 9) for dryness, foreign body sensation, burning, photophobia, and blurring

**07. Assessment for safety outcomes**: IOP and tolerability

**08. Planned follow-up duration**: 8 weeks

**09. Actual follow-up duration**: 8 weeks

**10. Planned treatment duration (of the intervention steroid)**: 8 weeks

**11. How missing data were handled**: NA

**12. Description on power and sample size calculation**: NR

Participants

**Country**: China

**Setting**: single medical center

**Intervention**:

- **Loteprednol etabonate (LE) 0.5% plus Liposic eye drops 0.2%**

Age, mean/SE (range): 36.4/4.5
Female, n (%): 11 (58%)
Etiology, n (%): NR
Participants (eyes) randomized: 19
Participants (eyes) analyzed for primary study outcomes: 19
Participants (eyes) analyzed for safety outcomes: 19

- **Cyclosporine A (CsA) 1% plus Liposic eye drops 0.2%**

Age, mean/SE (range): 33.6/5.0
Female, n (%): 10 (67%)
Etiology, n (%): NR
Participants (eyes) randomized: 15
Participants (eyes) analyzed for primary study outcomes: 15
Participants (eyes) analyzed for safety outcomes: 15

- **Overall**

**Wan 2012** *(Continued)*

Age, mean/SE (range): 35/5.0 (23 to 56)
Female, n (%): 21 (62%)
Etiology, n (%): NR
Participants (eyes) randomized: 34
Participants (eyes) analyzed for primary study outcomes: 34
Participants (eyes) analyzed for safety outcomes: 34

**Inclusion criteria**:

1. Diagnosis of dry eye without primary or secondary systemic conditions
2. Dry eye severity of 2 or 3 according to the TFOS Dry Eye Workshop grading system
3. Aged 18 to 60 years
4. No recent use of topical or systemic corticosteroid or non-steroidal hormone 1 week prior to the enrollment
5. Willing to sign the informed consent form

**Exclusion criteria**:

1. Major insufficiency in heart, brain, liver, or kidney
2. Pregnant or lactating women
3. Poor compliance

**Baseline comparison**: no statistical differences in baseline characteristics of the study participants (Table 1)

| | |
|---|---|
| Interventions | • **Loteprednol etabonate (LE) 0.5% plus Liposic eye drops 0.2%**, LE 2 times a day and Liposic 4 to 6 times a day<br>• **Cyclosporine A (CsA) 1% plus Liposic eye drops 0.2%**, CsA 2 times a day and Liposic 4 to 6 times a day |
| Outcomes | **Time points of primary outcome data collected**: weeks 2, 4, 6, and 8<br>**Primary outcomes of the study**:<br>1. Dry eye symptoms<br>2. Corneal fluorescein staining scores<br>3. Ocular surface inflammation<br>4. Conjunctival hyperemia (palpebral and bulbar), papillary reaction, follicle formation, conjunctival bulbar edema<br>**Other outcomes of the study**:<br>1. TBUT<br>2. Schirmer's test<br>3. IOP |
| Study Identification | **Sponsorship source**: National Natural Science Foundation (Grant no. 30973246), Provincial Science and Technology Research Grant (Grant no. 2009 A030200004), Provincial Medical Research and Development Fund (B2011106), Provincial Natural Science Foundation (S2011040004327)<br>**Ethics approval**: ethics approval requirement or process not reported<br>**Correspondence author's name**: Zungcze Wang; Institution: Chung Sang University Eye Center, Guangdong, China<br>**Additional information:**<br>1. Trial registration no.: NR |

**Wan 2012** *(Continued)*

2. Trial registration website: NR
3. Financial disclosure or conflicts of interest statement from authors: NR

| Notes |
|---|

AE, adverse event; ATS, artificial tear substitute; BCVA, best-corrected visual acuity; CAE, controlled adverse environment; CB, clobetasone butyrate; CI, confidence interval; CXCL10, C-X-C motif chemokine ligand 10; DE, dry eye; DED, dry eye disease; DEEP, Dry Eye Epidemiology Projects; ETDRS, Early Treatment of Diabetic Retinopathy Study; FML, fluorometholone; HLA-DR, human leukocyte antigen–DR isotype; IL-6, interleukin 6; IL-8, interleukin 8; IOP, intraocular pressure; IRB, institutional review board; ITT, intention-to-treat; IVCM, in vivo confocal microscopy; LASIK, laser in situ keratomileusis; MGD, meibomian gland dysfunction; NA, not applicable; NCT, clinical trial registry provided by the US National Library of Medicine; NEI, National Eye Institute; NIKBUT, non-invasive keratographic tear film break-up time; no., number; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs; OSDI, Ocular Surface Disease Index; OTC, over the counter; PVP, polyvinylpyrrolidone (tear substitute); SANDE, Symptom Assessment iN Dry Eye questionnaire; SD, standard deviation; SE, standard error; SPEED, Standard Patient Evaluation of Eye Dryness; SS, Sjögren syndrome; TBUT, tear film break-up time; TFOS, Tear Film & Ocular Surface Society; TNF-α, tumor necrosis factor-alpha; VAS, visual analogue scale

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

| Study | Reason for exclusion |
|---|---|
| Abud 2016 | Ineligible study population |
| Acord 2010 | Ineligible study design (cross-over trial, conference poster) |
| Asbell 2011 | Ineligible study design (workshop report) |
| Boynton 2015 | Ineligible study population |
| ChiCTR-IPQ-15006773 | Ineligible study design (quasi-randomization) |
| Edward 2014 | Trial withdrawn by sponsor (before participant enrollment) |
| EUCTR2006-003391-35-NL | Ineligible study design (within-person comparison) |
| EUCTR2019-000747-27-IT | Ineligible intervention (within-person comparison) |
| Gupta 2021 | Ineligible study design (review article) |
| ISRCTN13765551 | Ineligible study design (same intervention, preservative-free versus preserved formula) |
| Jee 2014 | Ineligible study design (same intervention, preservative-free versus preserved formula) |
| JPRN-UMIN000025159 | Ineligible study design (non-pharmacological intervention) |
| Kallab 2020 | Ineligible study design (comparing dosing schedules) |
| Korenfeld 2021 | Ineligible study design (secondary data analysis) |
| Lee 2006 | Ineligible study design (within-person comparison) |
| NCT03907865 | Ineligible study design (comparing dosing schedules) |
| Rolando 2008 | Ineligible study design (comparing dosing schedules) |
| Ryu 2005 | Ineligible study design (within-person comparison) |

| Study | Reason for exclusion |
|---|---|
| Shen 2015 | Ineligible intervention (FML combined with contact lens) |
| Sindhu 2015 | Ineligible study design (observational study) |
| Wong 2021 | Ineligible study design (review article) |

FML, fluorometholone

### Characteristics of studies awaiting classification *[ordered by study ID]*

**ChiCTR-IPR-15007196**

| | |
|---|---|
| Methods | Randomized parallel controlled trial |
| Participants | **Age limitation:** minimum 18; maximum 70<br><br>**Gender:** both (sex)<br><br>**Inclusion criteria:**<br><br>1. Voluntary participation in this clinical study, and signed informed consent<br>2. Sex is not limited, age 18 ~ 70 years of age<br>3. Clinical signs and symptoms of dry eye, clinical examination in accordance with the "dry eye expert consensus" diagnostic criteria (as follows):<br>a. there is dryness, foreign body sensation, burning sensation, fatigue, discomfort, visual fluctuation of subjective symptoms and BUT of less than 5 s or Schirmer I test (without surface anesthesia) less than 5 mm/5 min;<br>b. there is dryness, foreign body sensation, burning sensation, fatigue, discomfort, visual fluctuation of subjective symptoms and BUT between 5 to 10 s or 5 < Schirmer I test (without surface anesthesia) <= 10 mm/5 min. At the same time with conjunctival and corneal fluorescein staining.<br>4. Corneal fluorescein staining of 0 to I class and conjunctival fluorescein staining 0 to III grade<br>5. Regarding choice of study eyes: if participants were treated with both eyes, the eye with high symptom score was studied; in the case of an equal score, the corneal fluorescein staining more serious eye was studied; in the case of the degree of the same eyes fluorescein staining, the right eye was studied<br>6. Was not in clinical trials within 2 weeks<br>7. Other medications are not being used, or other drugs are being used but have been discontinued for more than 2 weeks<br><br>**Exclusion criteria:**<br><br>1. Any component of the test drug allergy<br>2. Pregnant or lactating women or recent fertility planners<br>3. Clinical diagnosis of fungal, bacterial, or viral angle, conjunctivitis active stage<br>4. The other conjunctiva, cornea andiris were significantly associated with the disease<br>5. Break-up time = 0 seconds, or Schirmer test < 2 mm/5 min<br>6. Patients with severe MGD (grade 4)<br>7. Combined with severe heart, cerebral blood vessel, liver, kidney, and hematopoietic system, and other serious diseases<br>8. Internal ocular surgery or ocular trauma in the past 6 months<br>9. Hormone replacement therapy for postmenopausal women<br>10.Accepting treatment of lacrimal point embolism in the last 1 month<br>11.Patients with herpes simplex keratitis infection<br>12.Treatment may affect the results of the study (e.g. systemic steroid, immunosuppressive therapy) |

**ChiCTR-IPR-15007196** *(Continued)*

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| | 13.Contact lens use was not stopped during the experiment<br>14.Patients with systemic or ocular conditions that require long-term use of medications that may affect research and evaluation<br>15.During the trial period, the drug was not guaranteed and followed up<br>16.Sjögren syndrome, systemic disease, and other ocular diseases that (may) affect efficacy (of the intervention)<br>17.The researchers considered that there was no reason for the test |
| Interventions | **Target sample size:** 40 in each group<br>1. 0.1% sodium bromide hydrate eyedrops + 0.1% sodium hyaluronate ophthalmic solution, 28 days<br>2. 0.1% pranoprofen eyedrops + 0.1% sodium hyaluronate ophthalmic solution, 28 days<br>3. 0.02% fluorometholone eye drops + 0.1% sodium hyaluronate ophthalmic solution, 28 days<br>4. Control group: 0.1% sodium hyaluronate ophthalmic solution, 28 days |
| Outcomes | **Primary outcomes:**<br>1. Tear meniscus height<br>2. TBUT3<br>3. Schirmer test<br>**Secondary outcomes:**<br>1. Corneal staining scores<br>2. Conjunctival staining scores |
| Notes | Sources of financial support: Senju Pharmaceutical Ltd<br>Date of first enrollment: 12 November 2015<br>Contacts: Zuguo Liu, Caihong Huang; Xiamen University, Fujian, China<br>Contact efforts made: emailed Dr Liu twice but no responses received within 2 weeks<br>Contact reasons: no trial results available |

**Herman 2005**

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|---|---|
| Methods | Randomized controlled trial, parallel group |
| Participants | Eligibility criteria not reported |
| Interventions | **Actual enrollment**: 30 participants in the steroid group, unknown number of participants in the control group<br>1. Prednisolone acetate 1.0% (Pred Forte)<br>2. Lubricant (Soothe Emollient) |
| Outcomes | 1. Staining scores<br>2. Symptom scores using a custom symptoms questionnaire (SPEED) |
| Notes | Sources of financial support: Ocular Research of Boston Inc and The Walter and Valerie Winchester Research Grant<br>Presented as ARVO Annual meeting abstract May 2005<br>Contacts efforts made: emailed JP Herman twice; no response received within 2 weeks<br>Contact reasons: the sample size of the control group was not reported in the conference abstract |

**NCT00471419**

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|---|---|
| Methods | Randomized parallel trial, double masking |
| Participants | **Sex:** all eligible for study<br>**Inclusion criteria:**<br>1. Documented dry eye history<br>2. Ocular symptoms<br>3. Tear use<br>4. Dry eye ocular signs<br>**Exclusion criteria:** under 18 years |
| Interventions | Estimated enrollment: 750 participants<br>1. Rimexolone<br>2. (Control intervention not reported) |
| Outcomes | **Primary outcomes:**<br>1. Corneal staining; dry eye symptom [ Time Frame: Immediate ]<br>**Secondary outcomes:**<br>1. Corneal staining; dry eye sympton [ Time Frame: Prolonged ] |
| Notes | Source of financial support: Alcon Research<br>Study start date: July 2006<br>Actual study completion date: August 2007<br>Investigator(s): Michael Brubaker, PhD; Alcon Research<br>Contact efforts made: emailed Alcon Research personnel 3 times; no responses received within 2 weeks<br>Contact reasons: unclear comparator treatment; no published trial results available |

**NCT00560638**

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|---|---|
| Methods | Randomized controlled trial, parallel assignment, double masked (participant and investigator) |
| Participants | **Sex:** all eligible for study<br>**Inclusion criteria:**<br>1. At least 18 years of age or older<br>2. Able and willing to follow instructions, including participation in study assessments and able to be present for the required study visits for the duration of the study<br>3. If female and of childbearing potential, were not pregnant, nursing, or planning a pregnancy. Women of childbearing potential were required to have a negative urine pregnancy test at the pre-screen visit and had to agree to use an acceptable method of mechanical or hormonal contraceptive for the duration of the study.<br>4. Diagnosis of dry eye<br>5. History of intermittent or regular artificial tear use within the past 3 months<br>6. BCVA of +0.7 or better assessed by ETDRS scale in 1 or both eyes<br>7. Fluorescein staining score of ≥ 1+ in at least 1 region in at least 1 eye at Visit 1 and before CAE exposure at Visits 2 and 3 OR a fluorescein staining score of ≥ 1+ in at least 1 region in at least 1 |

**NCT00560638** *(Continued)*

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| | eye at Visit 1 and before CAE exposure at Visits 2 and 3 with a conjunctival redness score of ≥ 1.5+ at Visit 1 and before CAE exposure at Visits 2 and 3 in at least 1 eye<br>8. Demonstrated a response when exposed to the CAE at Visits 2 and 3<br><br>Exclusion criteria:<br><br>1. Clinically significant blepharitis or MGD or lid margin inflammation, particularly if systemic or topical medications were currently being used to treat any of these diagnoses<br>2. Diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation (e.g. follicular conjunctivitis), or preauricular lymphadenopathy, particularly if systemic or topical medications were currently being used to treat any of these diagnoses<br>3. Reported an ocular discomfort score of 4+ in both eyes at time 0 of CAE exposure at Visits 2 or 3<br>4. Wore contact lenses and refused to remove them for the duration of the study<br>5. Previous LASIK surgery<br>6. Currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels, or scrubs and could not discontinue these medications for the duration of the study<br>7. Currently taking any medication known to cause ocular drying that had not been at a stable dose for at least 30 days<br>8. Currently taking oral antihistamines that could not be discontinued during the study<br>9. A systemic disease, uncontrolled medical condition that in the opinion of the investigator could interfere with study measurements or participant compliance<br>10. Received another experimental drug or device within 30 days prior to screening |
| Interventions | **Actual enrollment:** 119 participants<br><br>1. Loteprednol etabonate 0.5% (Lotemax) 3 times a day<br>2. Loteprednol etabonate 0.5% (Lotemax) 4 times a day<br>3. Vehicle of loteprednol etabonate 3 times a day<br>4. Vehicle of loteprednol etabonate 4 times a day |
| Outcomes | **Primary outcome measures:**<br><br>1. Ocular discomfort during CAE exposure [ Time Frame: during CAE exposure ]<br>2. Corneal and conjunctival staining and conjunctival redness [ Time Frame: after CAE exposure ]<br><br>**Secondary outcome measures:**<br><br>1. Corneal and conjunctival staining and conjunctival redness [ Time Frame: before CAE exposure ]<br>2. Blink rate, TBUT, and Ocular Protection Index [ Time Frame: before and after CAE exposure ]<br>3. Ocular discomfort [ Time Frame: collected in patient diaries ] |
| Notes | Source of financial support: Bausch & Lomb Inc<br>Study start date: November 2005<br>Actual study completion date: February 2006<br>Investigator(s): Gail Torkildsen MD; Ophthalmic Research Associates Inc<br>Contact efforts made: emailed to medical research personnel twice; no responses received within 2 weeks<br>Contact reasons: no trial results available |

**NCT01562795**

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| Methods | Randomized interventional trial, parallel group, open-label |

**NCT01562795** *(Continued)*

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| Participants | **Age:** 18 to 70 years<br><br>**Sex:** all eligible for study<br><br>**Inclusion criteria:**<br><br>1. Moderate to severe dry eye syndrome<br>2. TBUT > 0 s and ≤ 5 s, or Schirmer test (no anesthesia) ≥ 2 mm/5 min and ≤ 5 mm/5 min<br>3. Corneal staining ≥ 3 scores<br><br>**Exclusion criteria:**<br><br>1. Allergic to any composition of the drugs under experiment<br>2. Previous use of anti-inflammatory drugs or immunosuppressive agent<br>3. Viral, bacterial, or fungal infection of the eye<br>4. Eyelid anomaly<br>5. Glaucoma or high IOP<br>6. Significant MGD |
| Interventions | **Actual enrollment:** 48 participants<br><br>1. Group 1: non-steroidal anti-inflammatory drops (prunoprefen) plus artificial tear substitute<br>2. Group 2: non-steroidal anti-inflammatory drops (bronuck) plus artificial tear substitute<br>3. Group 3: corticosteroids (fluorometholone) plus artificial tear substitute<br>4. Group 4: artificial tear substitute alone |
| Outcomes | **Primary outcome measures:**<br><br>1. Tear osmolarity [ Time Frame: Day 0, Day 14 ]<br><br>**Secondary outcome measures:**<br><br>1. Corneal staining [ Time Frame: 0 day, 7th day, and 14th day after treatment ]<br>2. Schirmer test (without anesthesia) [ Time Frame: 0 day, 7th day, and 14th day after treatment ]<br>3. TBUT [ Time Frame: 0 day, 7th day, and 14th day after treatment ]<br>4. Meibomian gland function [ Time Frame: 0 day, 7th day, and 14th day after treatment ] |
| Notes | Sources of financial support: Wenzhou Medical University<br>Study start date: March 2012<br>Actual study completion date: July 2012<br>Investigator(s): Wei Chen, MD PhD; Eye Hospital, Wenzhou Medical College, China<br>Contact efforts made: emailed Dr Chen twice; no response received within 2 weeks<br>Contact reasons: the sample size of each group was not reported; no trial results available |

**NCT03418727**

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| Methods | Randomized parallel trial, double masking |
| Participants | **Sex:** all eligible for study<br><br>**Inclusion criteria:**<br><br>1. Aged 18 years or older<br>2. Sign and date informed consent form approved by the IRB<br>3. History of dry eye disease<br>4. Objective evidence of DED in at least 1 eye by having 2 or more of the following 4 signs in the same eye at Screening and Baseline (Day 1) visits: |

**NCT03418727** *(Continued)*

a. conjunctival staining at >/= 1 (out of a possible score of 6 per eye);
b. corneal staining at >/= 2 (out of a possible score of 15 per eye);
c. non-invasive tear break-up time at </= 7 seconds;
d. Schirmer test at < 10 mm in 5 minutes.

5. Symptomatic evidence of DED by having a global symptom score (SANDE) >/= 25 mm at both Screening and Baseline (Day 1) visits
6. Intraocular pressure >/= 5 mmHg and </= 22 mmHg in each eye
7. Women who satisfy 1 of the following:
   a. are of child-bearing potential (WOCP) who are not pregnant or lactating and who are either abstinent or sexually active on an acceptable method of birth control for at least 4 weeks prior to Visit 1 and throughout the study; OR
   b. are postmenopausal or have undergone a sterilization procedure.

**Exclusion criteria:**

1. Allergic to brimonidine, corticosteroids or any similar products, or excipients of brimonidine including benzalkonium chloride (BAK)
2. Use of contact lenses
3. Currently receiving brimonidine or other treatment for glaucoma or ocular hypertension or history of glaucoma surgery
4. Receiving or have received any experimental or investigational drug or device within 30 days prior to Screening visit
5. Intraocular pressure < 5 mmHg or > 22 mmHg in either eye
6. Active ocular infection or history of ocular herpetic keratitis
7. History of neurotrophic keratitis or ocular neuropathic pain
8. Any history of eyelid surgery or intraocular/ocular surgery within the past 3 months
9. Punctal occlusion within 3 months prior to Screening visit or during study
10. Corneal epithelial defect larger than 1 $mm^2$ in either eye
11. Have active drug/alcohol dependence or abuse history
12. Are neonates, pregnant/lactating women, children, institutionalized individuals, or others who may be considered vulnerable populations
13. Received corticosteroid-containing eyedrops within the past 7 days or systemic corticosteroids/immunosuppressives within the past 3 months
14. Received ciclosporin ophthalmic emulsion 0.05% (Restasis) or lifitegrast ophthalmic solution 5% (Xiidra) within 30 days prior to Screening visit
15. In the opinion of Investigator or Study Co-ordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eyedrops
16. Disease, condition, or disorder that in the judgement of Investigator could confound study assessments or limit compliance to study protocol

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| Interventions | **Actual enrollment:** 84 participants<br><br>1. Brimonidine followed by corticosteroid eyedrop, twice a day<br>2. Brimonidine followed by placebo drop twice a day<br>3. Placebo given twice a day |
| Outcomes | **Primary outcomes:** tolerability [ Time Frame: Baseline - Day 84 ]<br><br>Participants will assess their tolerance to the administration of the study drug, utilizing a VAS. The VAS is a 100-millimeter horizontal line with verbal descriptors at either end. The VAS ratings will be completed after administration of the study drug on day 1 (postdose), day 28, day 56, and day 84. Participants will place a single slash mark across the horizontal line between the end labeled "completely intolerable" (0 mm) and "easily tolerable" (100 mm). |
| Notes | Source of financial support: Ocugen<br>Study start date: September 2017<br>Actual study completion date: March 2018 |

**NCT03418727** *(Continued)*

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| | Investigator(s): Ocugen<br>Contact efforts made: contacted Ocugen research personnel twice; no response received within 2 weeks<br>Contact reasons: the specific type and concentration of interventional corticosteroid used was not reported; no trial results available |

**NTR2291**

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| Methods | Randomized, placebo-controlled, interventional trial, parallel group |
| Participants | **Inclusion criteria:**<br>1. Symptoms of dry eye<br>2. HLA-DR > 15%<br>3. At least 2 of the following:<br>a. Schirmer test < 8 mm/5 min;<br>b. TBUT < 10 s;<br>c. Lissamine green staining > 3.<br>**Exclusion criteria:**<br>1. Glaucoma<br>2. Ocular surface infections<br>3. Corneal ulcer<br>4. Conjunctival infections<br>5. Treatment with anti-inflammatory drugs in the 3 months preceding the study<br>6. Surgical procedures in the 3 months preceding the study<br>7. Antiglaucoma therapies<br>8. Contact lens use 7 days before the study |
| Interventions | **Target sample size:** 20<br>1. Loteprednolol etabonate 2 times a day for 14 days, once a day for 14 days, and twice a week for 28 days will be given at the study group (N = 10)<br>2. Artificial tear (carbossimetilcellulose) "with the same posology in the control group" (N = 10) |
| Outcomes | **Primary outcome:**<br>1. Reduced level of expression of HLA-DR after treatment with loteprednolol etabonate measured by flow cytometry<br>**Secondary outcomes:**<br>1. Reduced symptoms (measured by means of a specific questionnaire, OSDI)<br>2. Ocular surface signs (measured by fluorescein and Lissamine green staining of the ocular surface) after treatment of dry eye |
| Notes | Source of financial support: University of Genoa; Bausch & Lomb IOM<br>Start date: 1 January 2010<br>Stop date: 31 December 2010<br>Contact(s): Stefano Barabino, MD; Genoa, Italy<br>Contact efforts made: emailed Dr Barabino twice; no responses received within 2 weeks<br>Contact reasons: no trial results available |

BCVA, best-corrected visual acuity; BUT, break-up time; CAE, controlled adverse environment; DED, dry eye disease; ETDRS, Early Treatment of Diabetic Retinopathy Study; HLA-DR, human leukocyte antigen–DR isotype; IOP, intraocular pressure; IRB, Institutional Review Board;

LASIK, laser in situ keratomileusis; MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SANDE, Symptom Assessment iN Dry Eye questionnaire; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear film break-up time; VAS, visual analogue scale

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

**CTRI/2021/02/031182**

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| Study name | Eye drops made of antibodies for dry eye disease patients: topical human immunoglobulin as adjunct therapy in dry eye disease |
| Methods | • Randomized interventional placebo-controlled trial, parallel group<br>• Stratified block randomization<br>• Alternation blinding and masking (double masking) |
| Participants | **Country:** India<br><br>**Inclusion:**<br><br>1. IOP 5 to 22 mmHg in each eye<br>2. TBUT less than 7 seconds<br>3. Schirmer test less than 9 mm per 5 min<br>4. OSDI score of at least 13<br><br>**Exclusion:**<br><br>1. Patients not consenting to participate and follow up, presence of active systemic or ocular infections (including HBV, HCV, and HIV) at the time of initiation of therapy and history of recent ocular surgery in the preceding 6 weeks will not be included in the study<br>2. Allergic to IVIG or any similar products, or excipients of IVIG eyedrops 4 mg/mL<br>3. Use of contact lenses within the last 2 weeks prior to the baseline visit<br>4. Pregnant or nursing/lactating<br>5. Current diagnosis of any of the following ocular conditions: acute allergic conjunctivitis, active infection (e.g. bacterial, viral, protozoan or fungal infection of the cornea, conjunctiva, lacrimal gland, lacrimal sac or eyelids), active intraocular inflammation (e.g. retinitis, choroiditis, uveitis)<br>6. A cognitive or psychiatric deficit that precludes informed consent or ability to perform<br>7. Have active drug/alcohol dependence or abuse<br><br>**Target sample size:** 70 |
| Interventions | **Intervention:** topical immunoglobulin<br><br>1. Topical human IgG eyedrops (4 mg/mL) twice daily for 8 weeks (4 mg/mL)<br>2. Topical steroids (prednisolone acetate 1%) + antibiotic (chloramphenicol 1%/polymyxin eyedrops 5000 u/mL eyedrops) 3 times daily for 1 week<br>3. Topical carboxymethyl cellulose 4-hourly<br>4. Topical lubricant ointment at bedtime<br>5. Topical immunomodulators: CsA 0.1% eyedrops/tacrolimus 0.03% eye ointment<br><br>**Control intervention:** standard therapy for dry eye disease<br><br>1. Topical steroids (prednisolone acetate 1%) + antibiotic (chloramphenicol 1%/polymyxin eyedrops 5000 u/mL eyedrops) 3 times daily for 1 week<br>2. Topical carboxymethyl cellulose 4-hourly<br>3. Topical lubricant ointment at bedtime<br>4. Topical immunomodulators: CsA 0.1% eyedrops/tacrolimus 0.03% eye ointment |
| Outcomes | **Time point:** outcomes will be measured at baseline and time intervals: 1 and 2 months<br><br>**Primary outcomes:** |

**CTRI/2021/02/031182** *(Continued)*

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| | 1. Patient Complaint Score<br>2. UCVA, BCVA<br>3. OSDI score<br>4. Scores of the ocular surface evaluation tests: TBUT, NEI Corneal and Conjunctival Staining Score, Schirmer's I test, Conjunctival Injection Score, tear meniscometry, and tear osmolarity<br>5. Tear meniscometry<br><br>**Secondary outcomes:**<br>Changes in meibomian gland and tear imaging |
| Starting date | 1 March 2021 (date of first enrollment planned) |
| Contact information | Livia Khan; Institution: AIIMS, New Delhi<br><br>Prof DrM Vanathi; Institution: AIIMS, New Delhi |
| Notes | Status: not yet recruiting (as of 23 February 2021) |

**ISRCTN16288419**

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| Study name | Evaluation of the performance of new substitute tears in dry eye patients |
| Methods | Randomized interventional trial, double masked |
| Participants | **Country:** Italy<br><br>**Inclusion:**<br><br>1. Dry eye symptoms for at least 6 months, and 1 of the following signs:<br>a. corneal fluorescein staining = 3 (NEI grading scale);<br>b. conjunctival Lissamine green staining = 3 (NEI grading scale);<br>c. TBUT = 10 s.<br><br>**Exclusion:**<br><br>1. Patients changing systemic treatment during the study<br>2. Patients with ocular surface diseases other than dry eye<br>3. Pregnancy<br>4. Diabetes<br>5. Ocular surgery in the previous 3 months<br><br>**Target sample size:** 40 |
| Interventions | 1. Topical steroid FML twice daily and treatment (HA + 0.001% hydrocortisone) twice daily for 1 week<br>2. Control (HA alone) eyedrops twice daily for 1 week<br><br>At the end of the first week, participants will keep using eyedrops 4 times a day for 6 months. |
| Outcomes | **Time point:** outcomes will be measured at at day 7, 28, 56, 180<br><br>**Primary outcomes:**<br>Symptom improvement measured by SANDE score<br><br>**Secondary outcomes:**<br><br>1. Corneal fluorescein staining, NEI scale |

**ISRCTN16288419** *(Continued)*

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|---|---|
| | 2. Lissamine green conjunctival staining, NEI scale<br>3. TBUT, second<br>4. IOP, mmHg |
| Starting date | 10 June 2020 (date of first enrollment) |
| Contact information | Stefano Barabino; Institution: University of Milan, Italy |
| Notes | Current status: ongoing (as of 17 August 2020) |

**NCT04734197**

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|---|---|
| Study name | A research study to see how well an eye drop, SURF-100 (a mycophenolic acid/betamethasone sodium phosphate combination), works and what side effects there are in subjects with dry eye disease |
| Methods | • Randomized interventional placebo-controlled trial, parallel group<br>• Quadruple masking (participant, care provider, investigator, outcomes assessor) |
| Participants | **Country:** USA<br>**Inclusion:**<br>1. Adults at least 18 years of age at the time of the Screening Visit<br>2. Willing and able to read, sign, and date the informed consent form (ICF) after the nature of the study has been explained and any questions have been answered, and prior to initiation of any study procedures or exams<br>3. Willing and able to comply with all study procedures and attend all study visits<br>4. Willing to suspend use of tear substitutes at least 72 hours prior to Visit 2 (Day 0) through Visit 7 (Day 98)<br>5. BCVA of 0.7 log of the minimum angle of resolution (logMAR) or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1 (Day −14 to Day 0)<br>6. Participant-reported history of dry eye in both eyes<br>7. Meeting ALL of the following criteria in the same eye at Visit 1 (Day −14 to Day 0) and meeting ALL of the following criteria in the same eye at Visit 2 (Day 0) if Visit 2 is performed > 5 days after Visit 1:<br>a. minimum score of greater than or equal to 5 but less than or equal to 9 on UNC DEMS questionnaire;<br>b. Schirmer tear test (with anesthesia) equal to or less than 10 mm, but more than 1 mm;<br>c. TBUT: equal to or less than 5 seconds.<br>8. A negative urine pregnancy test if female and of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or postmenopausal [12 months after last menses] or premenarchal) and must have used adequate birth control throughout the study period (through Visit 7 [Day 98]). Adequate birth control is defined as hormonal: oral, implantable, injectable, or transdermal contraceptives; mechanical: spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; abstinence; or surgical sterilization of male partner<br>9. Patients with secondary Sjögren's syndrome (e.g. rheumatoid arthritis, systemic lupus erythematosus) or other autoimmune diseases (e.g. multiple sclerosis, inflammatory bowel disease) are eligible for study consideration provided they meet all other inclusion and exclusion criteria, AND are not in a medical state (in the opinion of the principal investigator) that could interfere with study parameters, are not taking systemic/ocular steroids, and are not immunodeficient/im- |

**NCT04734197** *(Continued)*

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| | munosuppressed (e.g. receiving systemic immunomodulating or immunosuppressive drugs to manage their baseline medical state)<br><br>**Exclusion:**<br><br>1. Contraindications or known hypersensitivity to the study drug(s), including Restasis or Xiidra, or their components<br>2. Patients who are employees or immediate family members of employees at the investigational site<br>3. Patients who are members of the same household<br>4. Any ocular condition that, in the opinion of the investigator, may affect study parameters including, but not limited to, lid margin disorders (e.g. blepharitis including staphylococcal, demodex, or seborrheic; excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, allergic conjunctivitis, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation (more extensive items on ClinicalTrials.gov)<br><br>**Target sample size:** 280 |
| Interventions | 1. Drug: combination of 0.3% mycophenolic acid and 0.01% betamethasone sodium phosphate<br>2. Drug: betamethasone sodium phosphate 0.01%<br>3. Drug: mycophenolic acid 0.3%<br>4. Drug: mycophenolic acid 0.1%<br>5. Drug: Restasis 0.05% Ophthalmic Emulsion<br>6. Drug: Xiidra 5% Ophthalmic Solution<br>7. Drug: placebo |
| Outcomes | **Time point:** outcomes will be measured at baseline and time intervals: day 84<br><br>**Primary outcomes:** UNC DEMS score [Time Frame: Day 84]<br>A reduction of 10% in patient-reported dry eye disease symptoms and reduction of impact of symptoms on daily life as defined by the UNC DEMS with SURF-100 as compared to vehicle, Restasis, and Xiidra<br><br>**Secondary outcomes:**<br><br>1. TBUT [Time Frame: Day 84]<br>2. Schirmer's tear test score [Time Frame: Day 84] |
| Starting date | 1 January 2021 (date of actual study start) |
| Contact information | Kamran Hosseini; Institution: Surface Pharmaceuticals Inc |
| Notes | Status: recruiting (as of 18 May 2021) |

**NCT04734210**

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|---|---|
| Study name | A research study to see how well an eye drop, SURF-200 (0.02% and 0.04% betamethasone sodium phosphate), works, what side effects there are, and to compare it with vehicle (placebo) in subjects diagnosed with dry eye disease and experiencing an episodic flare-up |
| Methods | • Randomized interventional placebo-controlled trial, parallel group<br>• Quadruple masking (participant, care provider, investigator, outcomes assessor) |

**NCT04734210** *(Continued)*

| | |
|---|---|
| Participants | **Country:** USA<br><br>**Inclusion:**<br><br>1. Patients 18 years of age and older who have a diagnosis of dry eye disease and are experiencing an episodic flare-up. Criteria for the diagnosis must include the following:<br>a. UNC DEMS score of greater than or equal to 5 but less than or equal to 9;<br>b. Conjunctival hyperemia score of greater than or equal to 2 in the study eye when using the conjunctival hyperemia reference photos;<br>c. Schirmer's tear test score (with anesthesia) greater than 1 mm but less than or equal to 12 mm in the study eye.<br>2. Patients must be able to understand and sign the informed consent form (ICF)<br>3. Females of childbearing potential must agree to and submit a negative urine pregnancy test before any study-specific procedures are performed. They must be using and continue to use a suitable method of contraception for the duration of the study: spermicide with barrier, oral contraceptive, transdermal contraceptive, injectable or implantable contraceptive, intrauterine device (IUD), abstinence, or surgical sterilization of a partner. If a female is not of childbearing potential (e.g. has been postmenopausal for at least 12 months or is premenarchal, or has undergone a hysterectomy, bilateral oophorectomy, or a bilateral tubal ligation), a urine pregnancy test and use of a suitable method of contraception for the duration of the study will not be required<br>4. Patients must have a BCVA of at least +1.0 log of the minimum angle of resolution (logMAR) (Snellen equivalent of 20/200) in the non-study eye (fellow eye)<br>5. Patients must have an IOP of > 8 mmHg and ≤ 22 mmHg in the study eye<br>6. Patients who are on Restasis, Xiidra, or other ciclosporin ophthalmic eye drops must be on a stable dose for at least 4 months prior to Screening Visit 1 (day −14 to day 0) and remain compliant with the use of these medications throughout the duration of the study<br>7. Patients who are on artificial tears, oral antihistamines, beta-blockers, and diuretics must be on a stable dose for at least 1 month prior to Screening Visit 1 (day −14 to day 0) and remain compliant with the use of these medications throughout the duration of the study<br>8. Patients must be willing and able to attend all study visits and follow all instructions<br>9. Patients must be able to self-instill the study drug (if unable, a caregiver must be available to instill all doses of the study drug)<br>10. Have a history of use or desire to use an eyedrop for dry eye symptoms for longer than the past 6 months<br><br>**Exclusion:**<br><br>1. Females who are pregnant or nursing or planning to become pregnant during the study. Females of childbearing potential (not surgically sterilized or postmenopausal) may not participate in the study if they do not agree to use adequate birth control methods for the duration of the study<br>2. Use of contact lenses in either eye during the study. Contact lens wear must have been discontinued at least 2 weeks prior to Baseline/Randomization Visit 2 (day 1).<br>3. Use of corticosteroids or non-steroidal anti-inflammatory agents (NSAIDs) (except oral doses of aspirin at 81 mg/day or lower) within 2 weeks of the initiation of study drug at Baseline/Randomization Visit 2 (day 1) and for the remainder of the study<br>4. Inhaled, ingested, sublingual, transdermal, or topical products containing marijuana, tetrahydrocannabinol (THC), or cannabidiol (CBD) within 7 days of the first dose of study drug at Baseline/Randomization Visit 2 (day 1) and for the remainder of the study<br>5. Presence or history of treatment with systemic immunosuppressive or chemotherapeutic agents<br>6. History of high IOP response to steroids<br>7. Participated in an ophthalmic investigational product clinical trial within 30 days of Screening Visit 1 (day −14 to day 0) (more extensive items on ClinicalTrials.gov)<br><br>**Target sample size:** 120 |
| Interventions | 1. Drug: 0.02% betamethasone sodium phosphate |

| | |
|---|---|
| **NCT04734210** *(Continued)* | 2. Drug: 0.04% betamethasone sodium phosphate<br>3. Drug: placebo (vehicle) |
| Outcomes | **Time point:** outcomes will be measured at baseline and time intervals: day 8<br><br>**Primary outcomes:** UNC DEMS score [Time Frame: Day 8]<br>A minimum reduction of 1 unit in patient-reported dry eye disease symptoms and reduction of impact of symptoms with SURF-200 as compared to vehicle (as measured by the UNC DEMS)<br><br>**Secondary outcomes:**<br><br>1. UNC DEMS score [ Time Frame: Day 15 ]: a minimum reduction of 1 unit in patient-reported dry eye disease symptoms and reduction of impact of symptoms with SURF-200 as compared to vehicle (as measured by the UNC DEMS)<br>2. Conjunctival hyperemia assessment [ Time Frame: Day 8 ]: a minimum reduction of 0.5 points in conjunctival hyperemia with SURF-200 as compared to vehicle using the Conjunctival Hyperemia Assessment 4-point scale (0 to 3) in the study eye |
| Starting date | 7 January 2021 (date of actual study start) |
| Contact information | Kamran Hosseini; Institution: Surface Pharmaceuticals Inc |
| Notes | Status: recruiting (as of 27 July 2021) |

ATS, artificial tear substitute; BCVA, best-corrected visual acuity; CAE, controlled adverse environment; CB, clobetasone butyrate; CsA, cyclosporine A; ETDRS, Early Treatment of Diabetic Retinopathy Study; FML, fluorometholone; HA, hyaluronic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; IOP, intraocular pressure; IVIG, intravenous immunoglobulin; LASIK, laser in situ keratomileusis; LE, loteprednol etabonate; MGD, meibomian gland dysfunction; MP, methylprednisolone; NA, not applicable; NCT, clinical trial registry provided by the US National Library of Medicine; NEI, National Eye Institute; no., number; NR, not reported; OSDI, Ocular Surface Disease Index; PVP, polyvinylpyrrolidone; SANDE, Symptom Assessment iN Dry Eye questionnaire; TBUT, tear film break-up time; UCVA, uncorrected visual acuity; UNC DEMS, University of North Carolina Dry Eye Management Scale

## RISK OF BIAS

**Legend:** ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

**Risk of bias for analysis 1.1 Patient-reported symptom scores—Qazi: LE alone**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Avunduk 2003 | ~ | ✓ | ~ | ✗ | ✗ | ✗ |
| Li 2021 | ~ | ~ | ✓ | ~ | ✗ | ✗ |
| Aragona 2013 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Lee 2014 | ✓ | ~ | ✓ | ✗ | ✗ | ✗ |

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Luo 2013 | ~ | ~ | ✓ | ✗ | ✓ | ✗ |
| Chen 2020 | ~ | ~ | ~ | ✗ | ~ | ✗ |
| Akhlaq 2019 | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (STRIDE1) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE3) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (Phase 2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE2) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| NCT01276223 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Qazi 2015 | ~ | ~ | ✓ | ✓ | ~ | ~ |
| Pflugfelder 2004 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Pinto-Fraga 2016 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |

**Risk of bias for analysis 1.3 Patient-reported symptom scores—Qazi: LE + tobramycin**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Avunduk 2003 | ~ | ✓ | ~ | ✗ | ✗ | ✗ |
| Li 2021 | ~ | ~ | ✓ | ~ | ✗ | ✗ |
| Aragona 2013 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Lee 2014 | ✓ | ~ | ✓ | ✗ | ✗ | ✗ |

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Luo 2013 | ~ | ~ | ✓ | ✗ | ✓ | ✗ |
| Chen 2020 | ~ | ~ | ~ | ✗ | ~ | ✗ |
| Akhlaq 2019 | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (STRIDE1) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE3) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (Phase 2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE2) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| NCT01276223 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Pflugfelder 2004 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Pinto-Fraga 2016 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Qazi 2015 | ~ | ~ | ✓ | ✓ | ~ | ~ |

**Risk of bias for analysis 1.13 Corneal fluorescein staining scores—Qazi: LE alone**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Cao 2018 | ~ | ~ | ✓ | ✗ | ✗ | ✗ |
| Pinto-Fraga 2016 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Li 2021 | ~ | ~ | ✓ | ✗ | ✗ | ✗ |
| Aragona 2013 | ~ | ✓ | ✓ | ✗ | ~ | ✗ |

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Akhlaq 2019 | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| Lee 2014 | ✓ | ~ | ✓ | ✓ | ✗ | ✗ |
| Avunduk 2003 | ~ | ✓ | ~ | ✓ | ~ | ~ |
| Chen 2020 | ~ | ~ | ✓ | ✗ | ~ | ✗ |
| KPI-121 (Phase 2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE3) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (STRIDE1) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Pflugfelder 2004 | ~ | ✓ | ✓ | ✗ | ~ | ~ |
| Qazi 2015 | ~ | ~ | ✓ | ✓ | ~ | ~ |
| Luo 2013 | ~ | ✓ | ✓ | ✗ | ✗ | ✗ |

**Risk of bias for analysis 1.15 Corneal fluorescein staining score—Qazi: LE + tobramycin**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Cao 2018 | ~ | ~ | ✓ | ✗ | ✗ | ✗ |
| Pinto-Fraga 2016 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Li 2021 | ~ | ~ | ✓ | ✗ | ✗ | ✗ |
| Aragona 2013 | ~ | ✓ | ✓ | ✗ | ~ | ✗ |

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Akhlaq 2019 | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| Lee 2014 | ✓ | ~ | ✓ | ✓ | ✗ | ✗ |
| Avunduk 2003 | ~ | ✓ | ~ | ✓ | ~ | ~ |
| Chen 2020 | ~ | ~ | ✓ | ✗ | ~ | ✗ |
| KPI-121 (Phase 2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE3) | ✓ | ✓ | ✓ | ✓ | ~ | ~ |
| KPI-121 (STRIDE1) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPI-121 (STRIDE2) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Pflugfelder 2004 | ~ | ✓ | ✓ | ✗ | ~ | ~ |
| Qazi 2015 | ~ | ~ | ✓ | ✓ | ~ | ~ |
| Luo 2013 | ~ | ✓ | ✓ | ✗ | ✗ | ✗ |

**Risk of bias for analysis 2.1 Patient-reported symptom scores—Bausch: LE alone**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Byun 2012 | ~ | ~ | ~ | ~ | ~ | ✗ |
| Singla 2019 | ~ | ✗ | ~ | ~ | ~ | ✗ |
| Wan 2012 | ~ | ✓ | ✓ | ✗ | ~ | ✗ |
| Sheppard 2014 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ |

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Lin 2015 | ~ | ~ | ✓ | ✗ | ~ | ✗ |
| Bausch 2013 | ~ | ✓ | ✓ | ✓ | ~ | ~ |

**Risk of bias for analysis 2.9 Corneal fluorescein staining scores—Bausch: LE alone**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Singla 2019 | ~ | ✗ | ~ | ✗ | ~ | ✗ |
| Byun 2012 | ~ | ~ | ~ | ✗ | ~ | ✗ |
| Wan 2012 | ~ | ✓ | ✓ | ✗ | ~ | ✗ |
| Sheppard 2014 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ |
| Bausch 2013 | ~ | ✓ | ✓ | ~ | ~ | ~ |
| Lin 2015 | ~ | ~ | ✓ | ✗ | ✓ | ✗ |

## DATA AND ANALYSES

### Comparison 1. Steroids versus lubricants

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Patient-reported symptom scores—Qazi: LE alone | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.29 [-0.42, -0.16] |
| 1.2 Patient-reported symptom scores—by questionnaire, Qazi: LE alone | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.29 [-0.42, -0.16] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.2.1 OSDI | 9 | 3238 | Std. Mean Difference (IV, Random, 95% CI) | -0.29 [-0.45, -0.13] |
| 1.2.2 Non-OSDI | 6 | 532 | Std. Mean Difference (IV, Random, 95% CI) | -0.30 [-0.56, -0.04] |
| 1.3 Patient-reported symptom scores—Qazi: LE + tobramycin | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.28 [-0.41, -0.14] |
| 1.4 Patient-reported symptom scores—by questionnaire, Qazi: LE + tobramycin | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.28 [-0.41, -0.14] |
| 1.4.1 OSDI | 9 | 3238 | Std. Mean Difference (IV, Random, 95% CI) | -0.27 [-0.44, -0.10] |
| 1.4.2 Non-OSDI | 6 | 532 | Std. Mean Difference (IV, Random, 95% CI) | -0.30 [-0.56, -0.04] |
| 1.5 Patient-reported symptom scores—by etiology | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.29 [-0.42, -0.16] |
| 1.5.1 Mixed patient populations | 11 | 3603 | Std. Mean Difference (IV, Random, 95% CI) | -0.26 [-0.40, -0.12] |
| 1.5.2 Patients with Sjögren Syndrome | 1 | 40 | Std. Mean Difference (IV, Random, 95% CI) | -0.76 [-1.40, -0.12] |
| 1.5.3 Patients with Meibomian Gland Dysfunction | 3 | 127 | Std. Mean Difference (IV, Random, 95% CI) | -0.42 [-0.77, -0.06] |
| 1.6 Patient-reported symptom scores—by risk of bias | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.6.1 Low/some concerns RoB | 10 | 3263 | Std. Mean Difference (IV, Random, 95% CI) | -0.19 [-0.28, -0.10] |
| 1.6.2 High RoB | 5 | 507 | Std. Mean Difference (IV, Random, 95% CI) | -0.63 [-0.84, -0.43] |
| 1.7 Patient-reported symptom scores—by sponsorship | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.7.1 Industry or affiliation & industry | 10 | 3300 | Std. Mean Difference (IV, Random, 95% CI) | -0.17 [-0.27, -0.07] |
| 1.7.2 University or government | 3 | 245 | Std. Mean Difference (IV, Random, 95% CI) | -0.49 [-0.75, -0.24] |
| 1.7.3 Not reported | 2 | 262 | Std. Mean Difference (IV, Random, 95% CI) | -0.78 [-1.05, -0.50] |
| 1.8 Patient-reported symptom scores—by regimen and steroid type | 15 | 3807 | Std. Mean Difference (IV, Random, 95% CI) | -0.27 [-0.40, -0.14] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.8.1 (Ester) steroid alone | 9 | 3198 | Std. Mean Difference (IV, Random, 95% CI) | -0.22 [-0.31, -0.13] |
| 1.8.2 (Ketone) steroid alone | 5 | 542 | Std. Mean Difference (IV, Random, 95% CI) | -0.44 [-0.90, 0.02] |
| 1.8.3 (Ester) steroid plus antiseptic/antimicrobial | 1 | 37 | Std. Mean Difference (IV, Random, 95% CI) | 0.39 [-0.26, 1.04] |
| 1.8.4 (Ketone) steroid plus antiseptic/antimicrobial | 1 | 30 | Std. Mean Difference (IV, Random, 95% CI) | -0.43 [-1.15, 0.30] |
| 1.9 Patient-reported symptom scores—by steroid treatment duration | 15 | 3770 | Std. Mean Difference (IV, Random, 95% CI) | -0.29 [-0.42, -0.16] |
| 1.9.1 Short-term (< 28 days) | 5 | 2751 | Std. Mean Difference (IV, Random, 95% CI) | -0.20 [-0.31, -0.10] |
| 1.9.2 Long-term (28 to 42 days) | 9 | 959 | Std. Mean Difference (IV, Random, 95% CI) | -0.36 [-0.60, -0.11] |
| 1.9.3 Long-term > 42 days | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -0.62 [-1.14, -0.10] |
| 1.10 Tear film break-up time—Qazin: LE alone | 7 | 935 | Mean Difference (IV, Random, 95% CI) | 0.70 [0.23, 1.17] |
| 1.11 Tear film break-up time—Qazi: LE + tobramycin | 7 | 935 | Mean Difference (IV, Random, 95% CI) | 0.78 [0.34, 1.21] |
| 1.12 Tear film break-up time—by steroid type | 7 | 935 | Mean Difference (IV, Random, 95% CI) | 0.70 [0.23, 1.17] |
| 1.12.1 Loterprednol etabonate (LE): Ketone steroid | 4 | 391 | Mean Difference (IV, Random, 95% CI) | 0.85 [-0.48, 2.17] |
| 1.12.2 Fluorometholone (FML)/Clobetasol (CB): Ester steroid | 3 | 544 | Mean Difference (IV, Random, 95% CI) | 0.52 [0.32, 0.71] |
| 1.13 Corneal fluorescein staining scores—Qazi: LE alone | 15 | 3699 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.62, -0.18] |
| 1.14 Corneal fluorescein staining score—by grading system, Qazi: LE alone | 15 | 3699 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.62, -0.18] |
| 1.14.1 NEI grading | 7 | 2940 | Std. Mean Difference (IV, Random, 95% CI) | -0.14 [-0.22, -0.07] |
| 1.14.2 Other grading systems | 8 | 759 | Std. Mean Difference (IV, Random, 95% CI) | -0.51 [-1.04, 0.01] |
| 1.15 Corneal fluorescein staining score—Qazi: LE + tobramycin | 15 | 3699 | Std. Mean Difference (IV, Random, 95% CI) | -0.39 [-0.61, -0.17] |

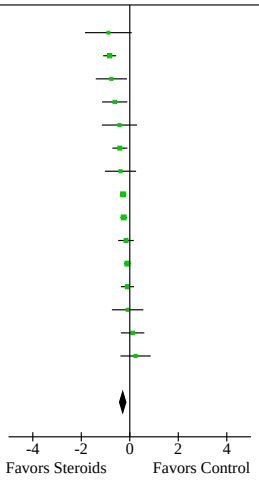
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.16 Corneal fluorescein staining score—by grading system, Qazi: LE + tobramycin | 15 | 3699 | Std. Mean Difference (IV, Random, 95% CI) | -0.39 [-0.61, -0.17] |
| 1.16.1 NEI grading | 7 | 2940 | Std. Mean Difference (IV, Random, 95% CI) | -0.14 [-0.22, -0.07] |
| 1.16.2 Other grading systems | 8 | 759 | Std. Mean Difference (IV, Random, 95% CI) | -0.47 [-1.01, 0.07] |
| 1.17 Corneal fluorescein staining scores—by etiology | 15 | 3699 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.62, -0.18] |
| 1.17.1 Mixed patient population | 11 | 3532 | Std. Mean Difference (IV, Random, 95% CI) | -0.50 [-0.74, -0.25] |
| 1.17.2 Patients with Sjögren syndrome | 1 | 40 | Std. Mean Difference (IV, Random, 95% CI) | -0.60 [-1.24, 0.03] |
| 1.17.3 Patients with Meibomian Gland Dysfunction | 3 | 127 | Std. Mean Difference (IV, Random, 95% CI) | 0.17 [-0.61, 0.96] |
| 1.18 Corneal fluorescein staining score—by risk of bias | 15 | 3736 | Std. Mean Difference (IV, Random, 95% CI) | -0.36 [-0.58, -0.15] |
| 1.18.1 Low/some concerns RoB | 10 | 3120 | Std. Mean Difference (IV, Random, 95% CI) | -0.20 [-0.34, -0.06] |
| 1.18.2 High RoB | 5 | 616 | Std. Mean Difference (IV, Random, 95% CI) | -0.52 [-1.21, 0.18] |
| 1.19 Corneal fluorescein staining score—by sponsorship | 15 | 3736 | Std. Mean Difference (IV, Random, 95% CI) | -0.36 [-0.58, -0.15] |
| 1.19.1 Industry or affiliation & industry | 9 | 3101 | Std. Mean Difference (IV, Random, 95% CI) | -0.20 [-0.34, -0.05] |
| 1.19.2 University or government | 3 | 245 | Std. Mean Difference (IV, Random, 95% CI) | -0.35 [-0.60, -0.10] |
| 1.19.3 Not reported | 3 | 390 | Std. Mean Difference (IV, Random, 95% CI) | -0.58 [-1.87, 0.70] |
| 1.20 Corneal fluorescein staining score—by steroid treatment duration | 15 | 3736 | Std. Mean Difference (IV, Random, 95% CI) | -0.36 [-0.58, -0.15] |
| 1.20.1 Short-term (< 28 days) | 5 | 2763 | Std. Mean Difference (IV, Random, 95% CI) | -0.15 [-0.38, 0.07] |
| 1.20.2 Short-term (28 to 42 days) | 9 | 913 | Std. Mean Difference (IV, Random, 95% CI) | -0.46 [-0.84, -0.07] |
| 1.20.3 Duration ≥ 2 months | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -0.42 [-0.93, 0.09] |

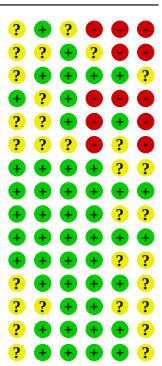
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.21 Tear osmolarity | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 1.22 Schirmer's test—Qazi: LE alone | 5 | 541 | Mean Difference (IV, Random, 95% CI) | 0.94 [0.39, 1.49] |
| 1.23 Schirmer's test—Qazi: LE + tobramycin | 5 | 541 | Mean Difference (IV, Random, 95% CI) | 0.69 [-0.02, 1.39] |
| 1.24 Schirmer test—by steroid type, Qazi: LE alone | 5 | 541 | Mean Difference (IV, Random, 95% CI) | 0.94 [0.39, 1.49] |
| 1.24.1 Loteprednol etabonate (LE): Ketone steroid | 3 | 269 | Mean Difference (IV, Random, 95% CI) | 1.44 [0.88, 1.99] |
| 1.24.2 Fluorometholone (FML): Ester steroid | 2 | 272 | Mean Difference (IV, Random, 95% CI) | 0.61 [0.30, 0.92] |
| 1.25 Schirmer test—by steroid type, Qazi: LE + tobramycin | 5 | 541 | Mean Difference (IV, Random, 95% CI) | 0.69 [-0.02, 1.39] |
| 1.25.1 Loteprednol etabonate (LE): Ketone steroid | 3 | 269 | Mean Difference (IV, Random, 95% CI) | 0.54 [-1.21, 2.30] |
| 1.25.2 Fluorometholone (FML): Ester steroid | 2 | 272 | Mean Difference (IV, Random, 95% CI) | 0.61 [0.30, 0.92] |
| 1.26 Proportion of participants with increased IOP—by steroid type | 8 | 2264 | Risk Ratio (M-H, Random, 95% CI) | 5.96 [1.30, 27.38] |
| 1.26.1 Ester steroid: LE | 4 | 1954 | Risk Ratio (M-H, Random, 95% CI) | 3.59 [0.59, 21.97] |
| 1.26.2 Ketone steroids | 4 | 310 | Risk Ratio (M-H, Random, 95% CI) | 20.42 [1.21, 344.00] |
| 1.27 Proportion of participants with new cataract formation | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.28 Proportion of participants with serious adverse events (systemic or ocular) | 4 | 2167 | Risk Ratio (M-H, Fixed, 95% CI) | 3.03 [0.82, 11.13] |

## Analysis 1.1. Comparison 1: Steroids versus lubricants, Outcome 1: Patient-reported symptom scores—Qazi: LE alone

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Avunduk 2003 (1) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.6% | -0.88 [-1.85 , 0.08] |
| Li 2021 (2) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.2% | -0.83 [-1.10 , -0.56] |
| Aragona 2013 (3) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.2% | -0.76 [-1.40 , -0.12] |
| Lee 2014 (4) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.5% | -0.62 [-1.14 , -0.10] |
| Luo 2013 (5) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] |
| Chen 2020 (6) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] |
| Akhlaq 2019 (7) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.2% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (8) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 13.0% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (8) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.9% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (9) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (8) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.9% | -0.10 [-0.23 , 0.03] |
| NCT01276223 (10) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Qazi 2015 (11) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] |
| Pflugfelder 2004 (12) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] |
| Pinto-Fraga 2016 (13) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.29 [-0.42 , -0.16]** |

Heterogeneity: Tau² = 0.03; Chi² = 36.86, df = 14 (P = 0.0008); I² = 62%
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable




**Footnotes**

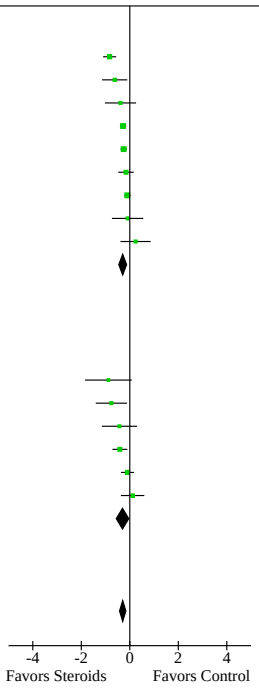
(1) At day 30, dry eye screening questionnaire for DEEP; FML (conc. unknown)
(2) At week 4, FML 0.1%; unit of analysis was eye
(3) At day 30, VAS; CB 0.1%
(4) At month 2, LE 0.5%
(5) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(6) At month 1, LE 0.1%
(7) At week 6, OSDI; LE 0.5%
(8) At day 14, OSDI; LE 0.25%
(9) At day 28, OSDI; LE 0.25%
(10) At week 4, VAS; difluprednate 0.05%
(11) At week 4, OSDI; LE 0.5%
(12) At week 4, VAS; LE 0.5%
(13) At day 21, OSDI; FML 0.1%

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.2. Comparison 1: Steroids versus lubricants, Outcome 2: Patient-reported symptom scores—by questionnaire, Qazi: LE alone

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|---|---|
| **1.2.1 OSDI** | | | | | | | | | |
| Li 2021 (1) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.2% | -0.83 [-1.10 , -0.56] | ? ? + - ? - |
| Lee 2014 (2) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.5% | -0.62 [-1.14 , -0.10] | + ? + - - - |
| Akhlaq 2019 (3) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.2% | -0.38 [-1.03 , 0.26] | + + + + ? ? |
| KPI-121 (STRIDE1) (4) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 13.0% | -0.28 [-0.41 , -0.15] | + + + + + + |
| KPI-121 (STRIDE3) (4) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.9% | -0.25 [-0.38 , -0.12] | + + + + ? ? |
| KPI-121 (Phase 2) (5) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] | + + + + + + |
| KPI-121 (STRIDE2) (4) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.9% | -0.10 [-0.23 , 0.03] | + + + + ? ? |
| Qazi 2015 (6) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] | ? + + + ? ? |
| Pinto-Fraga 2016 (7) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] | ? + + + + + |
| **Subtotal (95% CI)** | | | **1609** | | | **1629** | **70.2%** | **-0.29 [-0.45 , -0.13]** | |
| Heterogeneity: Tau² = 0.03; Chi² = 28.07, df = 8 (P = 0.0005); I² = 72% | | | | | | | | | |
| Test for overall effect: Z = 3.56 (P = 0.0004) | | | | | | | | | |
| **1.2.2 Non-OSDI** | | | | | | | | | |
| Avunduk 2003 (8) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.6% | -0.88 [-1.85 , 0.08] | ? + + ? - - |
| Aragona 2013 (9) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.2% | -0.76 [-1.40 , -0.12] | ? + + + + ? |
| Luo 2013 (10) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] | ? ? + - + - |
| Chen 2020 (11) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] | ? ? ? - ? - |
| NCT01276223 (12) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] | ? + + + + ? |
| Pflugfelder 2004 (13) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] | ? + + + + ? |
| **Subtotal (95% CI)** | | | **268** | | | **264** | **29.8%** | **-0.30 [-0.56 , -0.04]** | |
| Heterogeneity: Tau² = 0.04; Chi² = 8.79, df = 5 (P = 0.12); I² = 43% | | | | | | | | | |
| Test for overall effect: Z = 2.29 (P = 0.02) | | | | | | | | | |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.29 [-0.42 , -0.16]** | |
| Heterogeneity: Tau² = 0.03; Chi² = 36.86, df = 14 (P = 0.0008); I² = 62% | | | | | | | | | |
| Test for overall effect: Z = 4.37 (P < 0.0001) | | | | | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0% | | | | | | | | | |




**Footnotes**

(1) At week 4; unit of analysis eye
(2) At month 2
(3) At week 6
(4) At day 14
(5) At day 28
(6) At week 4
(7) At day 21
(8) At day 30, dry eye screening questionnaire for DEEP; data extracted from graphical readings
(9) At day 30, VAS with a scale of 0 to 100
(10) At week 1, a 6-point symptom questionnaire was used
(11) At month 1; SPEED questionnaire with a scale of 0 to 100 to assess 6 symptoms
(12) At week 4, VAS with a scale of 0 to 100 for each of 6 symptoms
(13) At week 4, VAS with a scale of 0 to 100 and a composite scores summing of severity and frequency of symptoms (0 to 200)

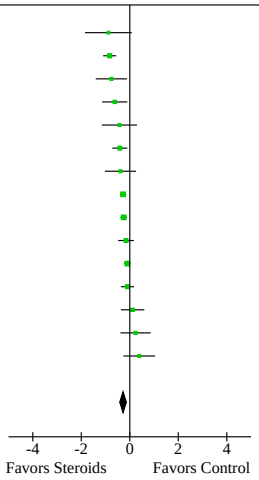
**Risk of bias legend**

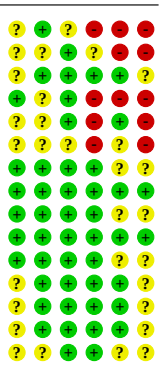
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.3. Comparison 1: Steroids versus lubricants, Outcome 3: Patient-reported symptom scores—Qazi: LE + tobramycin

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Avunduk 2003 (1) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.8% | -0.88 [-1.85 , 0.08] |
| Li 2021 (2) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.1% | -0.83 [-1.10 , -0.56] |
| Aragona 2013 (3) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.4% | -0.76 [-1.40 , -0.12] |
| Lee 2014 (4) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.7% | -0.62 [-1.14 , -0.10] |
| Luo 2013 (5) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.8% | -0.43 [-1.15 , 0.30] |
| Chen 2020 (6) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] |
| Akhlaq 2019 (7) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.4% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (8) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 12.5% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (8) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.5% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (9) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (8) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.5% | -0.10 [-0.23 , 0.03] |
| NCT01276223 (10) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Pflugfelder 2004 (11) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 5.1% | 0.12 [-0.37 , 0.60] |
| Pinto-Fraga 2016 (12) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.6% | 0.24 [-0.38 , 0.86] |
| Qazi 2015 (13) | 56.6 | 22.4 | 17 | 48.4 | 18.9 | 20 | 3.3% | 0.39 [-0.26 , 1.04] |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.28 [-0.41 , -0.14]** |

Heterogeneity: Tau² = 0.03; Chi² = 40.32, df = 14 (P = 0.0002); I² = 65%
Test for overall effect: Z = 3.98 (P < 0.0001)
Test for subgroup differences: Not applicable




**Footnotes**

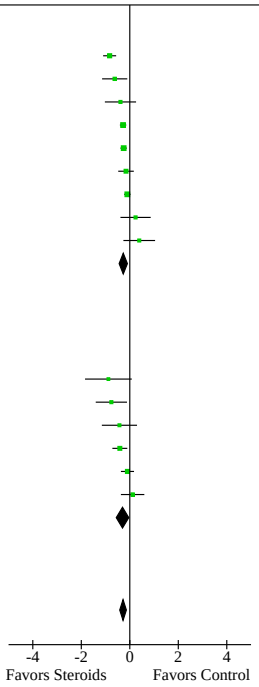
(1) At day 30, dry eye screening quesitonnaire for DEEP; FML (conc. unknown)
(2) At week 4, FML 0.1%; unit of analysis was eye (N=116, 232 eyes)
(3) At day 30, VAS; CB 0.1%
(4) At month 2, LE 0.5%
(5) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(6) At month 1, LE 0.1%
(7) At week 6, OSDI change scores; LE 0.5%
(8) At day 14, OSDI change scores; LE 0.25%
(9) At day 28, OSDI; LE 0.25%
(10) At week 4, VAS change scores; difluprednate 0.05%
(11) At week 4, VAS change scores; LE 0.5%
(12) At day 21, OSDI change scores; FML 0.1%
(13) At week 4, OSDI; LE 0.5% + tobramycin

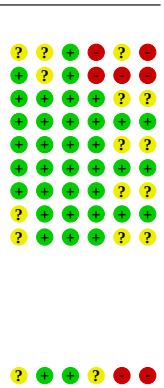
**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.4. Comparison 1: Steroids versus lubricants, Outcome 4: Patient-reported symptom scores—by questionnaire, Qazi: LE + tobramycin

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.4.1 OSDI** | | | | | | | | |
| Li 2021 (1) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.1% | -0.83 [-1.10 , -0.56] |
| Lee 2014 (2) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.7% | -0.62 [-1.14 , -0.10] |
| Akhlaq 2019 (3) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.4% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (4) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 12.5% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (4) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.5% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (5) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (4) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.5% | -0.10 [-0.23 , 0.03] |
| Pinto-Fraga 2016 (6) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.6% | 0.24 [-0.38 , 0.86] |
| Qazi 2015 (7) | 56.6 | 22.4 | 17 | 48.4 | 18.9 | 20 | 3.3% | 0.39 [-0.26 , 1.04] |
| **Subtotal (95% CI)** | | | **1609** | | | **1629** | **69.5%** | **-0.27 [-0.44 , -0.10]** |
| Heterogeneity: Tau² = 0.04; Chi² = 31.52, df = 8 (P = 0.0001); I² = 75% | | | | | | | | |
| Test for overall effect: Z = 3.09 (P = 0.002) | | | | | | | | |
| **1.4.2 Non-OSDI** | | | | | | | | |
| Avunduk 2003 (8) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.8% | -0.88 [-1.85 , 0.08] |
| Aragona 2013 (9) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.4% | -0.76 [-1.40 , -0.12] |
| Luo 2013 (10) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.8% | -0.43 [-1.15 , 0.30] |
| Chen 2020 (11) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] |
| NCT01276223 (12) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Pflugfelder 2004 (13) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 5.1% | 0.12 [-0.37 , 0.60] |
| **Subtotal (95% CI)** | | | **268** | | | **264** | **30.5%** | **-0.30 [-0.56 , -0.04]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.79, df = 5 (P = 0.12); I² = 43% | | | | | | | | |
| Test for overall effect: Z = 2.29 (P = 0.02) | | | | | | | | |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.28 [-0.41 , -0.14]** |
| Heterogeneity: Tau² = 0.03; Chi² = 40.32, df = 14 (P = 0.0002); I² = 65% | | | | | | | | |
| Test for overall effect: Z = 3.98 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0% | | | | | | | | |




**Footnotes**

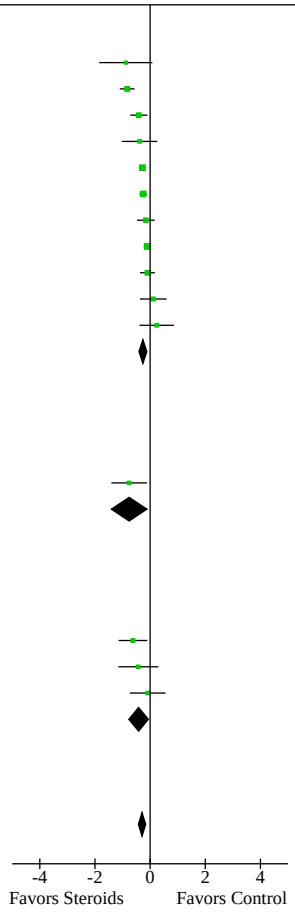
(1) At week 4; unit of analysis eye
(2) At month 2
(3) At week 6
(4) At day 14
(5) At day 28
(6) At day 21
(7) At week 4
(8) At day 30, dry eye screening questionnaire for DEEP; data extracted from graphical readings
(9) At day 30, VAS with a scale of 0 to 100
(10) At week 1, a 6-point symptom questionnaire was used
(11) At month 1; SPEED questionnaire with a scale of 0 to 100 to assess 6 symptoms
(12) At week 4, VAS with a scale of 0 to 100 for each of 6 symptoms
(13) At week 4, VAS with a scale of 0 to 100 and a composite scores summing of severity and frequency of symptoms (0 to 200)

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.5. Comparison 1: Steroids versus lubricants, Outcome 5: Patient-reported symptom scores—by etiology

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 Mixed patient populations** | | | | | | | | |
| Avunduk 2003 (1) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.6% | -0.88 [-1.85 , 0.08] |
| Li 2021 (2) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.2% | -0.83 [-1.10 , -0.56] |
| Chen 2020 (3) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] |
| Akhlaq 2019 (4) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.2% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (5) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 13.0% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (5) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.9% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (6) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (5) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.9% | -0.10 [-0.23 , 0.03] |
| NCT01276223 (7) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Pflugfelder 2004 (8) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] |
| Pinto-Fraga 2016 (9) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] |
| **Subtotal (95% CI)** | | | **1795** | | | **1808** | **86.4%** | **-0.26 [-0.40 , -0.12]** |
| Heterogeneity: Tau² = 0.03; Chi² = 31.96, df = 10 (P = 0.0004); I² = 69% | | | | | | | | |
| Test for overall effect: Z = 3.60 (P = 0.0003) | | | | | | | | |
| **1.5.2 Patients with Sjögren Syndrome** | | | | | | | | |
| Aragona 2013 (10) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.2% | -0.76 [-1.40 , -0.12] |
| **Subtotal (95% CI)** | | | **20** | | | **20** | **3.2%** | **-0.76 [-1.40 , -0.12]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.31 (P = 0.02) | | | | | | | | |
| **1.5.3 Patients with Meibomian Gland Dysfunction** | | | | | | | | |
| Lee 2014 (11) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.5% | -0.62 [-1.14 , -0.10] |
| Luo 2013 (12) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] |
| Qazi 2015 (13) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] |
| **Subtotal (95% CI)** | | | **62** | | | **65** | **10.4%** | **-0.42 [-0.77 , -0.06]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.31 (P = 0.02) | | | | | | | | |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.29 [-0.42 , -0.16]** |
| Heterogeneity: Tau² = 0.03; Chi² = 36.86, df = 14 (P = 0.0008); I² = 62% | | | | | | | | |
| Test for overall effect: Z = 4.37 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.67, df = 2 (P = 0.26), I² = 25.0% | | | | | | | | |

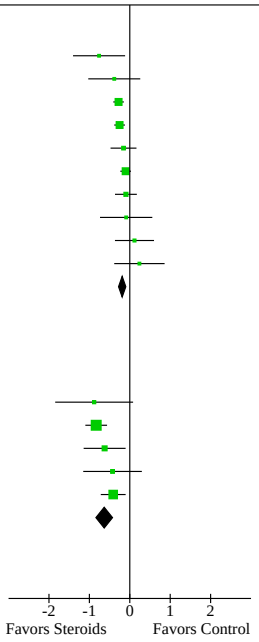


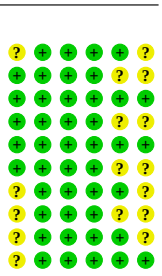

**Footnotes**

(1) At day 30, dry eye screening questionnaire for DEEP; FML (conc. unknown)
(2) At week 4, FML 0.1%; unit of analysis was eye
(3) At month 1, LE 0.1%
(4) At week 6, OSDI; LE 0.5%
(5) At day 14, OSDI; LE 0.25%
(6) At day 28, OSDI; LE 0.25%
(7) At week 4, VAS; difluprednate 0.05%
(8) At week 4, VAS; LE 0.5%
(9) At day 21, OSDI; FML 0.1%
(10) At day 30, VAS; CB 0.1%
(11) At month 2, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(13) At week 4, OSDI; LE 0.5%

# Analysis 1.6. Comparison 1: Steroids versus lubricants, Outcome 6: Patient-reported symptom scores—by risk of bias

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.6.1 Low/some concerns RoB** | | | | | | | | |
| Aragona 2013 (1) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 1.9% | -0.76 [-1.40 , -0.12] |
| Akhlaq 2019 (2) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 1.9% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (3) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 24.5% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (3) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 24.3% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (4) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 6.8% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (3) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 24.4% | -0.10 [-0.23 , 0.03] |
| NCT01276223 (5) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Qazi 2015 (6) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 1.9% | -0.09 [-0.74 , 0.56] |
| Pflugfelder 2004 (7) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 3.2% | 0.12 [-0.37 , 0.60] |
| Pinto-Fraga 2016 (8) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 2.0% | 0.24 [-0.38 , 0.86] |
| **Subtotal (95% CI)** | | | **1622** | | | **1641** | **100.0%** | **-0.19 [-0.28 , -0.10]** |
| Heterogeneity: Tau² = 0.00; Chi² = 11.57, df = 9 (P = 0.24); I² = 22% | | | | | | | | |
| Test for overall effect: Z = 4.10 (P < 0.0001) | | | | | | | | |
| **1.6.2 High RoB** | | | | | | | | |
| Avunduk 2003 (9) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 4.4% | -0.88 [-1.85 , 0.08] |
| Li 2021 (10) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 40.6% | -0.83 [-1.10 , -0.56] |
| Lee 2014 (11) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 14.0% | -0.62 [-1.14 , -0.10] |
| Luo 2013 (12) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 7.6% | -0.43 [-1.15 , 0.30] |
| Chen 2020 (13) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 33.4% | -0.41 [-0.72 , -0.10] |
| **Subtotal (95% CI)** | | | **255** | | | **252** | **100.0%** | **-0.63 [-0.84 , -0.43]** |
| Heterogeneity: Tau² = 0.01; Chi² = 4.67, df = 4 (P = 0.32); I² = 14% | | | | | | | | |
| Test for overall effect: Z = 6.03 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 15.08, df = 1 (P = 0.0001), I² = 93.4% | | | | | | | | |




**Footnotes**

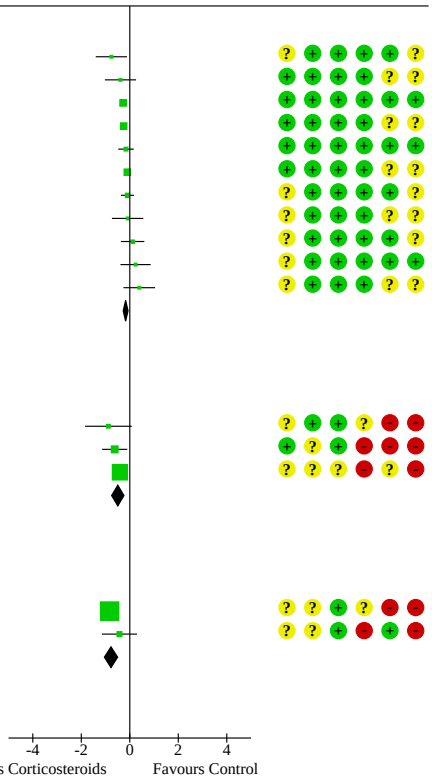
(1) At day 30, VAS; CB 0.1%
(2) At week 6, OSDI; LE 0.5%
(3) At day 14, OSDI; LE 0.25%
(4) At day 28, OSDI; LE 0.25%
(5) At week 4, VAS; difluprednate 0.05%
(6) At week 4, OSDI; LE 0.5%
(7) At week 4, VAS; LE 0.5%
(8) At day 21, OSDI; FML 0.1%
(9) At day 30, dry eye screening questionnaire for DEEP; FML
(10) At week 4, FML 0.1%, unit of analysis was eye
(11) At month 2, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(13) At month 1, LE 0.1%

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.7. Comparison 1: Steroids versus lubricants, Outcome 7: Patient-reported symptom scores—by sponsorship

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.7.1 Industry or affiliation & industry** | | | | | | | | |
| Aragona 2013 (1) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 2.3% | -0.76 [-1.40 , -0.12] |
| Akhlaq 2019 (2) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 2.3% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (3) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 22.4% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (3) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 22.2% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (4) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.7% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (3) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 22.3% | -0.10 [-0.23 , 0.03] |
| NCT01276223 (5) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 10.0% | -0.10 [-0.37 , 0.17] |
| Qazi 2015 (6) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 2.3% | -0.09 [-0.74 , 0.56] |
| Pflugfelder 2004 (7) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 3.9% | 0.12 [-0.37 , 0.60] |
| Pinto-Fraga 2016 (8) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 2.4% | 0.24 [-0.38 , 0.86] |
| Qazi 2015 (9) | 56.6 | 22.4 | 17 | 48.4 | 18.9 | 20 | 2.2% | 0.39 [-0.26 , 1.04] |
| **Subtotal (95% CI)** | | | **1639** | | | **1661** | **100.0%** | **-0.17 [-0.27 , -0.07]** |
| Heterogeneity: Tau² = 0.01; Chi² = 14.62, df = 10 (P = 0.15); I² = 32% | | | | | | | | |
| Test for overall effect: Z = 3.35 (P = 0.0008) | | | | | | | | |
| **1.7.2 University or government** | | | | | | | | |
| Avunduk 2003 (10) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 7.0% | -0.88 [-1.85 , 0.08] |
| Lee 2014 (11) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 24.2% | -0.62 [-1.14 , -0.10] |
| Chen 2020 (12) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 68.8% | -0.41 [-0.72 , -0.10] |
| **Subtotal (95% CI)** | | | **124** | | | **121** | **100.0%** | **-0.49 [-0.75 , -0.24]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.56); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.80 (P = 0.0001) | | | | | | | | |
| **1.7.3 Not reported** | | | | | | | | |
| Li 2021 (13) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 86.1% | -0.83 [-1.10 , -0.56] |
| Luo 2013 (14) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 13.9% | -0.43 [-1.15 , 0.30] |
| **Subtotal (95% CI)** | | | **131** | | | **131** | **100.0%** | **-0.78 [-1.05 , -0.50]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² = 5% | | | | | | | | |
| Test for overall effect: Z = 5.55 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 19.70, df = 2 (P < 0.0001), I² = 89.8% | | | | | | | | |







**Footnotes**

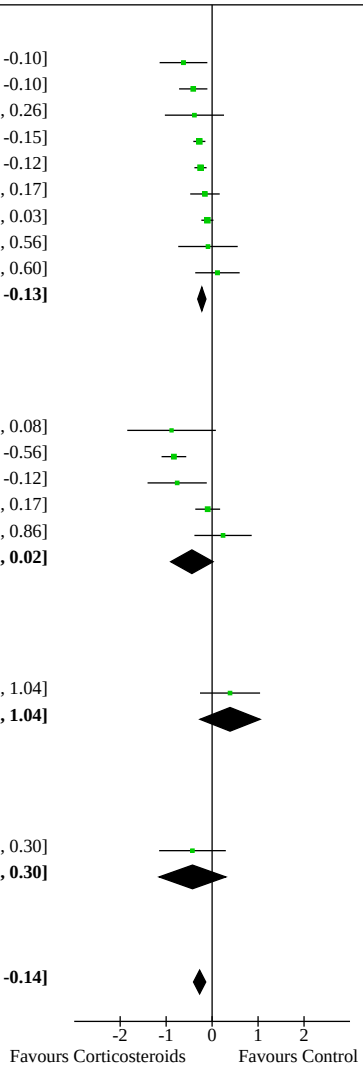
(1) At day 30, VAS; CB 0.1%
(2) At week 6, OSDI; LE 0.5%
(3) At day 14, OSDI; LE 0.25%
(4) At day 28, OSDI; LE 0.25%
(5) At week 4, VAS; difluprednate 0.05%
(6) At week 4, OSDI; LE 0.5%
(7) At week 4, VAS; LE 0.5%
(8) At day 21, OSDI; FML 0.1%
(9) At week 4, OSDI; LE 0.5% + tobramycin vs. artificial tears
(10) At day 30, dry eye screening questionnaire for DEEP; FML (conc. unknown)
(11) At month 2, LE 0.5%
(12) At month 1, LE 0.1%
(13) At week 4, FML 0.1%; unit of analysis was eye
(14) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.8. Comparison 1: Steroids versus lubricants, Outcome 8: Patient-reported symptom scores—by regimen and steroid type

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.8.1 (Ester) steroid alone** | | | | | | | | |
| Lee 2014 (1) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.4% | -0.62 [-1.14 , -0.10] |
| Chen 2020 (2) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.0% | -0.41 [-0.72 , -0.10] |
| Akhlaq 2019 (3) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.3% | -0.38 [-1.03 , 0.26] |
| KPI-121 (STRIDE1) (4) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 12.2% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (4) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.2% | -0.25 [-0.38 , -0.12] |
| KPI-121 (Phase 2) (5) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.7% | -0.16 [-0.48 , 0.17] |
| KPI-121 (STRIDE2) (4) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.2% | -0.10 [-0.23 , 0.03] |
| Qazi 2015 (6) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] |
| Pflugfelder 2004 (6) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] |
| **Subtotal (95% CI)** | | | **1587** | | | **1611** | **68.1%** | **-0.22 [-0.31 , -0.13]** |
| Heterogeneity: Tau² = 0.00; Chi² = 10.24, df = 8 (P = 0.25); I² = 22% | | | | | | | | |
| Test for overall effect: Z = 4.90 (P < 0.00001) | | | | | | | | |
| **1.8.2 (Ketone) steroid alone** | | | | | | | | |
| Avunduk 2003 (7) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.7% | -0.88 [-1.85 , 0.08] |
| Li 2021 (8) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 8.9% | -0.83 [-1.10 , -0.56] |
| Aragona 2013 (9) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.3% | -0.76 [-1.40 , -0.12] |
| NCT01276223 (10) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 8.8% | -0.10 [-0.37 , 0.17] |
| Pinto-Fraga 2016 (11) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] |
| **Subtotal (95% CI)** | | | **275** | | | **267** | **26.0%** | **-0.44 [-0.90 , 0.02]** |
| Heterogeneity: Tau² = 0.20; Chi² = 20.70, df = 4 (P = 0.0004); I² = 81% | | | | | | | | |
| Test for overall effect: Z = 1.87 (P = 0.06) | | | | | | | | |
| **1.8.3 (Ester) steroid plus antiseptic/antimicrobial** | | | | | | | | |
| Qazi 2015 (12) | 56.6 | 22.4 | 17 | 48.4 | 18.9 | 20 | 3.2% | 0.39 [-0.26 , 1.04] |
| **Subtotal (95% CI)** | | | **17** | | | **20** | **3.2%** | **0.39 [-0.26 , 1.04]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | | | |
| **1.8.4 (Ketone) steroid plus antiseptic/antimicrobial** | | | | | | | | |
| Luo 2013 (13) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] |
| **Subtotal (95% CI)** | | | **15** | | | **15** | **2.7%** | **-0.43 [-1.15 , 0.30]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.15 (P = 0.25) | | | | | | | | |
| **Total (95% CI)** | | | **1894** | | | **1913** | **100.0%** | **-0.27 [-0.40 , -0.14]** |
| Heterogeneity: Tau² = 0.03; Chi² = 40.55, df = 15 (P = 0.0004); I² = 63% | | | | | | | | |
| Test for overall effect: Z = 4.01 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 4.54, df = 3 (P = 0.21), I² = 33.9% | | | | | | | | |

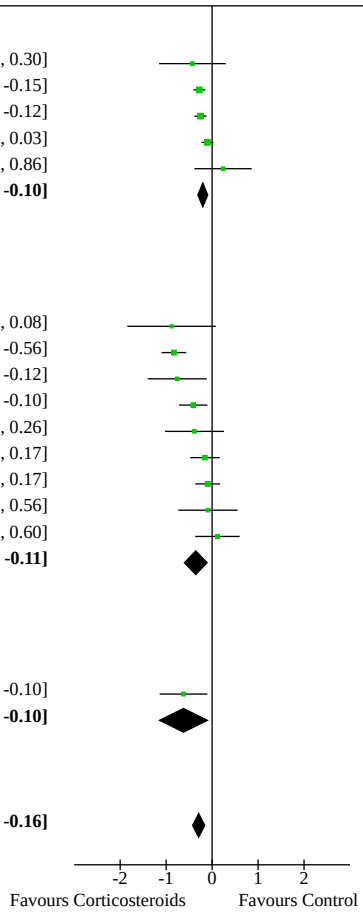



**Footnotes**

(1) At month 2, LE 0.5%
(2) At month 1, LE 0.1%
(3) At week 6, LE 0.5%
(4) At day 14, LE 0.25%
(5) At day 28, LE 0.25%
(6) At week 4, LE 0.5%
(7) At day 30, FML (conc. unknown)
(8) At week 4, FML 0.1%; unit of analysis was eye
(9) At day 30, CB 0.1%
(10) At week 4, difluprednate 0.05%
(11) At day 21, FML 0.1%
(12) At week 4, LE 0.5% + tobramycin
(13) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin

## Analysis 1.9. Comparison 1: Steroids versus lubricants, Outcome 9: Patient-reported symptom scores—by steroid treatment duration

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.9.1 Short-term (< 28 days)** | | | | | | | | |
| Luo 2013 (1) | 1.1 | 0.91 | 15 | 1.46 | 0.72 | 15 | 2.7% | -0.43 [-1.15 , 0.30] |
| KPI-121 (STRIDE1) (2) | -14.53 | 20.64 | 455 | -9.16 | 17.92 | 452 | 13.0% | -0.28 [-0.41 , -0.15] |
| KPI-121 (STRIDE3) (2) | -13.58 | 19.38 | 434 | -8.91 | 17.58 | 451 | 12.9% | -0.25 [-0.38 , -0.12] |
| KPI-121 (STRIDE2) (2) | -11.14 | 19.9 | 445 | -9.24 | 17 | 444 | 12.9% | -0.10 [-0.23 , 0.03] |
| Pinto-Fraga 2016 (3) | -0.08 | 3.33 | 21 | -0.94 | 3.76 | 19 | 3.4% | 0.24 [-0.38 , 0.86] |
| **Subtotal (95% CI)** | | | **1370** | | | **1381** | **44.9%** | **-0.20 [-0.31 , -0.10]** |
| Heterogeneity: Tau² = 0.00; Chi² = 6.31, df = 4 (P = 0.18); I² = 37% | | | | | | | | |
| Test for overall effect: Z = 3.71 (P = 0.0002) | | | | | | | | |
| **1.9.2 Long-term (28 to 42 days)** | | | | | | | | |
| Avunduk 2003 (4) | -9 | 4.57 | 11 | -4.78 | 4.57 | 8 | 1.6% | -0.88 [-1.85 , 0.08] |
| Li 2021 (5) | 32.3 | 9.1 | 116 | 39.57 | 8.32 | 116 | 9.2% | -0.83 [-1.10 , -0.56] |
| Aragona 2013 (4) | 150.1 | 127.6 | 20 | 238.6 | 98.8 | 20 | 3.2% | -0.76 [-1.40 , -0.12] |
| Chen 2020 (6) | 10.27 | 1.73 | 83 | 11.07 | 2.13 | 83 | 8.2% | -0.41 [-0.72 , -0.10] |
| Akhlaq 2019 (7) | -8.41 | 29.2 | 18 | 1.59 | 21.6 | 20 | 3.2% | -0.38 [-1.03 , 0.26] |
| KPI-121 (Phase 2) (8) | 57.05 | 23.89 | 73 | 60.47 | 19.77 | 77 | 7.9% | -0.16 [-0.48 , 0.17] |
| NCT01276223 (9) | -6.2 | 15.1 | 107 | -4.7 | 16.1 | 104 | 9.1% | -0.10 [-0.37 , 0.17] |
| Qazi 2015 (9) | 46.4 | 24.8 | 17 | 48.4 | 18.9 | 20 | 3.2% | -0.09 [-0.74 , 0.56] |
| Pflugfelder 2004 (9) | -31.58 | 24.8 | 32 | -34.55 | 25.7 | 34 | 4.9% | 0.12 [-0.37 , 0.60] |
| **Subtotal (95% CI)** | | | **477** | | | **482** | **50.6%** | **-0.36 [-0.60 , -0.11]** |
| Heterogeneity: Tau² = 0.08; Chi² = 24.18, df = 8 (P = 0.002); I² = 67% | | | | | | | | |
| Test for overall effect: Z = 2.83 (P = 0.005) | | | | | | | | |
| **1.9.3 Long-term > 42 days** | | | | | | | | |
| Lee 2014 (10) | 6.94 | 10.46 | 30 | 13.54 | 10.46 | 30 | 4.5% | -0.62 [-1.14 , -0.10] |
| **Subtotal (95% CI)** | | | **30** | | | **30** | **4.5%** | **-0.62 [-1.14 , -0.10]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.35 (P = 0.02) | | | | | | | | |
| **Total (95% CI)** | | | **1877** | | | **1893** | **100.0%** | **-0.29 [-0.42 , -0.16]** |
| Heterogeneity: Tau² = 0.03; Chi² = 36.86, df = 14 (P = 0.0008); I² = 62% | | | | | | | | |
| Test for overall effect: Z = 4.37 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.41, df = 2 (P = 0.18), I² = 41.3% | | | | | | | | |



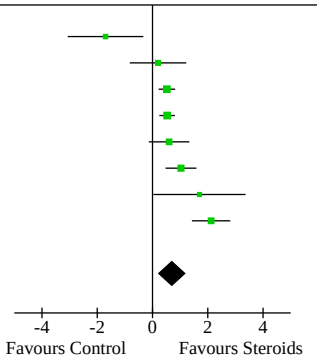

**Footnotes**

(1) At week 1
(2) At day 14
(3) At day 21
(4) At day 30
(5) At week 4; unit of analysis was eye
(6) At month 1
(7) At week 6
(8) At day 28
(9) At week 4
(10) At month 2

## Analysis 1.10. Comparison 1: Steroids versus lubricants, Outcome 10: Tear film break-up time—Qazin: LE alone

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Qazi 2015 (1) | 2.5 | 0.8 | 17 | 4.2 | 3 | 20 | 7.3% | -1.70 [-3.07 , -0.33] |
| Pinto-Fraga 2016 (2) | 2.9 | 1.95 | 21 | 2.7 | 1.31 | 19 | 10.0% | 0.20 [-0.82 , 1.22] |
| Li 2021 (3) | 5.61 | 1.17 | 116 | 5.09 | 1.16 | 116 | 17.7% | 0.52 [0.22 , 0.82] |
| Li 2021 (4) | 6.9 | 1.19 | 116 | 6.37 | 0.99 | 116 | 17.9% | 0.53 [0.25 , 0.81] |
| Aragona 2013 (5) | 1 | 1.25 | 20 | 0.4 | 1.11 | 20 | 13.0% | 0.60 [-0.13 , 1.33] |
| Chen 2020 (6) | 5.36 | 1.84 | 83 | 4.33 | 1.83 | 83 | 15.0% | 1.03 [0.47 , 1.59] |
| Lee 2014 (7) | 9.85 | 3.29 | 30 | 8.15 | 3.29 | 30 | 5.6% | 1.70 [0.04 , 3.36] |
| Cao 2018 (8) | 14.29 | 2.06 | 64 | 12.17 | 1.95 | 64 | 13.5% | 2.12 [1.43 , 2.81] |
| **Total (95% CI)** | | | **467** | | | **468** | **100.0%** | **0.70 [0.23 , 1.17]** |

Heterogeneity: Tau² = 0.30; Chi² = 34.00, df = 7 (P < 0.0001); I² = 79%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable

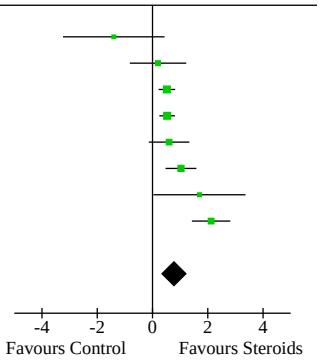



**Footnotes**
(1) At week 4, LE 0.5%
(2) At day 21, FML 0.1%
(3) At week 4, FML 0.1%; unit of analysis was eye
(4) At week 4, FML 0.1%; unit of analysis was eye; NIKBUT measurements
(5) At day 30, CB 0.1%
(6) At month 1, LE 0.1%
(7) At month 2, LE 0.5%
(8) At week 6, LE (conc. unknown)

## Analysis 1.11. Comparison 1: Steroids versus lubricants, Outcome 11: Tear film break-up time—Qazi: LE + tobramycin

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Qazi 2015 (1) | 2.8 | 2.7 | 17 | 4.2 | 3 | 20 | 4.4% | -1.40 [-3.24 , 0.44] |
| Pinto-Fraga 2016 (2) | 2.9 | 1.95 | 21 | 2.7 | 1.31 | 19 | 9.7% | 0.20 [-0.82 , 1.22] |
| Li 2021 (3) | 5.61 | 1.17 | 116 | 5.09 | 1.16 | 116 | 19.2% | 0.52 [0.22 , 0.82] |
| Li 2021 (4) | 6.9 | 1.19 | 116 | 6.37 | 0.99 | 116 | 19.4% | 0.53 [0.25 , 0.81] |
| Aragona 2013 (5) | 1 | 1.25 | 20 | 0.4 | 1.11 | 20 | 13.1% | 0.60 [-0.13 , 1.33] |
| Chen 2020 (6) | 5.36 | 1.84 | 83 | 4.33 | 1.83 | 83 | 15.6% | 1.03 [0.47 , 1.59] |
| Lee 2014 (7) | 9.85 | 3.29 | 30 | 8.15 | 3.29 | 30 | 5.1% | 1.70 [0.04 , 3.36] |
| Cao 2018 (8) | 14.29 | 2.06 | 64 | 12.17 | 1.95 | 64 | 13.6% | 2.12 [1.43 , 2.81] |
| **Total (95% CI)** | | | **467** | | | **468** | **100.0%** | **0.78 [0.34 , 1.21]** |

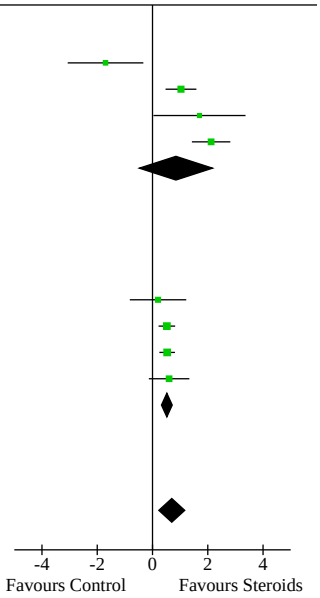
Heterogeneity: Tau² = 0.23; Chi² = 27.43, df = 7 (P = 0.0003); I² = 74%
Test for overall effect: Z = 3.52 (P = 0.0004)
Test for subgroup differences: Not applicable




**Footnotes**
(1) At week 4, LE 0.5% + tobramycin 0.3%
(2) At day 21, FML 0.1%
(3) At week 4, FML 0.1%; unit of analysis was eye
(4) At week 4, FML 0.1%; unit of analysis was eye; NIKBUT measurements
(5) At day 30, CB 0.1%
(6) At month 1, LE 0.1%
(7) At month 2, LE 0.5%
(8) At week 6, LE (conc. unknown)

## Analysis 1.12. Comparison 1: Steroids versus lubricants, Outcome 12: Tear film break-up time—by steroid type

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.12.1 Loterprednol etabonate (LE): Ketone steroid** | | | | | | | | |
| Qazi 2015 (1) | 2.5 | 0.8 | 17 | 4.2 | 3 | 20 | 7.3% | -1.70 [-3.07 , -0.33] |
| Chen 2020 (2) | 5.36 | 1.84 | 83 | 4.33 | 1.83 | 83 | 15.0% | 1.03 [0.47 , 1.59] |
| Lee 2014 (3) | 9.85 | 3.29 | 30 | 8.15 | 3.29 | 30 | 5.6% | 1.70 [0.04 , 3.36] |
| Cao 2018 (4) | 14.29 | 2.06 | 64 | 12.17 | 1.95 | 64 | 13.5% | 2.12 [1.43 , 2.81] |
| **Subtotal (95% CI)** | | | **194** | | | **197** | **41.4%** | **0.85 [-0.48 , 2.17]** |
| Heterogeneity: Tau² = 1.51; Chi² = 24.68, df = 3 (P < 0.0001); I² = 88% | | | | | | | | |
| Test for overall effect: Z = 1.25 (P = 0.21) | | | | | | | | |
| **1.12.2 Fluorometholone (FML)/Clobetasol (CB): Ester steroid** | | | | | | | | |
| Pinto-Fraga 2016 (5) | 2.9 | 1.95 | 21 | 2.7 | 1.31 | 19 | 10.0% | 0.20 [-0.82 , 1.22] |
| Li 2021 (6) | 5.61 | 1.17 | 116 | 5.09 | 1.16 | 116 | 17.7% | 0.52 [0.22 , 0.82] |
| Li 2021 (7) | 6.9 | 1.19 | 116 | 6.37 | 0.99 | 116 | 17.9% | 0.53 [0.25 , 0.81] |
| Aragona 2013 (8) | 1 | 1.25 | 20 | 0.4 | 1.11 | 20 | 13.0% | 0.60 [-0.13 , 1.33] |
| **Subtotal (95% CI)** | | | **273** | | | **271** | **58.6%** | **0.52 [0.32 , 0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (P = 0.93); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 5.24 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **467** | | | **468** | **100.0%** | **0.70 [0.23 , 1.17]** |
| Heterogeneity: Tau² = 0.30; Chi² = 34.00, df = 7 (P < 0.0001); I² = 79% | | | | | | | | |
| Test for overall effect: Z = 2.91 (P = 0.004) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0% | | | | | | | | |



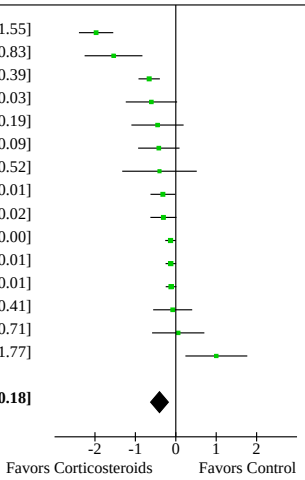

**Footnotes**

(1) At week 4, LE 0.5%
(2) At month 1, LE 0.1%
(3) At month 2, LE 0.5%
(4) At week 6, LE
(5) At day 21, FML 0.1%
(6) At week 4, FML 0.1%; unit of analysis was eye
(7) At week 4, FML 0.1%; unit of analysis was eye; NIKBUT measurements
(8) At day 30, CB 0.1%

## Analysis 1.13. Comparison 1: Steroids versus lubricants, Outcome 13: Corneal fluorescein staining scores—Qazi: LE alone

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cao 2018 (1) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 7.0% | -1.97 [-2.40 , -1.55] | ? | ? | + | - | - | - |
| Pinto-Fraga 2016 (2) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.7% | -1.54 [-2.26 , -0.83] | ? | + | + | + | + | ? |
| Li 2021 (3) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 8.4% | -0.66 [-0.92 , -0.39] | ? | ? | + | - | - | - |
| Aragona 2013 (4) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.3% | -0.60 [-1.24 , 0.03] | ? | + | + | - | ? | - |
| Akhlaq 2019 (5) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.2% | -0.45 [-1.10 , 0.19] | + | + | + | + | ? | ? |
| Lee 2014 (6) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.3% | -0.42 [-0.93 , 0.09] | + | ? | + | + | - | - |
| Avunduk 2003 (7) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.5% | -0.40 [-1.33 , 0.52] | ? | + | ? | + | ? | ? |
| Chen 2020 (8) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 8.0% | -0.32 [-0.63 , -0.01] | ? | ? | + | - | ? | - |
| KPI-121 (Phase 2) (9) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.9% | -0.31 [-0.63 , 0.02] | + | + | + | + | + | + |
| KPI-121 (STRIDE3) (10) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 9.2% | -0.13 [-0.26 , 0.00] | + | + | + | + | ? | ? |
| KPI-121 (STRIDE1) (10) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 9.2% | -0.12 [-0.25 , 0.01] | + | + | + | + | + | + |
| KPI-121 (STRIDE2) (10) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 9.2% | -0.12 [-0.25 , 0.01] | + | + | + | + | + | + |
| Pflugfelder 2004 (11) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.5% | -0.08 [-0.56 , 0.41] | ? | + | + | - | ? | ? |
| Qazi 2015 (11) | 5 | 3.3 | 17 | 4.8 | 3.2 | 20 | 5.2% | 0.06 [-0.59 , 0.71] | ? | ? | + | + | ? | ? |
| Luo 2013 (12) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.4% | 1.00 [0.24 , 1.77] | ? | + | + | - | - | - |
| **Total (95% CI)** | | | **1840** | | | **1859** | **100.0%** | **-0.40 [-0.62 , -0.18]** | | | | | | |

Heterogeneity: Tau² = 0.13; Chi² = 109.41, df = 14 (P < 0.00001); I² = 87%
Test for overall effect: Z = 3.62 (P = 0.0003)
Test for subgroup differences: Not applicable




**Footnotes**

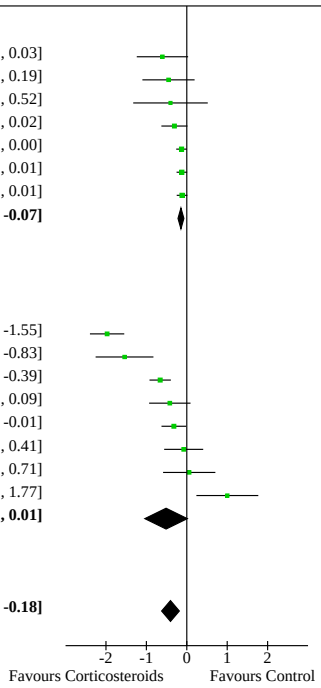
(1) At week 6, LE (conc. unknown)
(2) At day 21, FML 01%, Oxford grading scheme and Waterloo grading system
(3) At week 4, FML 0.1%; unit of analysis was eye
(4) At day 30, CB 0.1%, NEI grading
(5) At week 6, LE 0.5%, NEI grading
(6) At month 2, LE
(7) At day 30, FML, NEI grading
(8) At month 1, LE 0.1%
(9) At day 28, LE 0.25%, NEI grading
(10) At day 14, LE 0.25%, NEI grading change scores
(11) At week 4, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin, grading according to Macri and Qiu

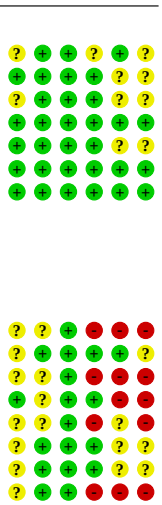
**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.14. Comparison 1: Steroids versus lubricants, Outcome 14: Corneal fluorescein staining score—by grading system, Qazi: LE alone

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.14.1 NEI grading** | | | | | | | | |
| Aragona 2013 (1) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.3% | -0.60 [-1.24 , 0.03] |
| Akhlaq 2019 (2) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.2% | -0.45 [-1.10 , 0.19] |
| Avunduk 2003 (3) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.5% | -0.40 [-1.33 , 0.52] |
| KPI-121 (Phase 2) (4) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.9% | -0.31 [-0.63 , 0.02] |
| KPI-121 (STRIDE3) (5) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 9.2% | -0.13 [-0.26 , 0.00] |
| KPI-121 (STRIDE1) (5) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 9.2% | -0.12 [-0.25 , 0.01] |
| KPI-121 (STRIDE2) (5) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 9.2% | -0.12 [-0.25 , 0.01] |
| **Subtotal (95% CI)** | | | **1462** | | | **1478** | **49.5%** | **-0.14 [-0.22 , -0.07]** |
| Heterogeneity: Tau² = 0.00; Chi² = 4.46, df = 6 (P = 0.61); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.92 (P < 0.0001) | | | | | | | | |
| **1.14.2 Other grading systems** | | | | | | | | |
| Cao 2018 (6) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 7.0% | -1.97 [-2.40 , -1.55] |
| Pinto-Fraga 2016 (7) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.7% | -1.54 [-2.26 , -0.83] |
| Li 2021 (8) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 8.4% | -0.66 [-0.92 , -0.39] |
| Lee 2014 (9) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.3% | -0.42 [-0.93 , 0.09] |
| Chen 2020 (10) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 8.0% | -0.32 [-0.63 , -0.01] |
| Pflugfelder 2004 (11) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.5% | -0.08 [-0.56 , 0.41] |
| Qazi 2015 (11) | 5 | 3.3 | 17 | 4.8 | 3.2 | 20 | 5.2% | 0.06 [-0.59 , 0.71] |
| Luo 2013 (12) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.4% | 1.00 [0.24 , 1.77] |
| **Subtotal (95% CI)** | | | **378** | | | **381** | **50.5%** | **-0.51 [-1.04 , 0.01]** |
| Heterogeneity: Tau² = 0.50; Chi² = 76.01, df = 7 (P < 0.00001); I² = 91% | | | | | | | | |
| Test for overall effect: Z = 1.91 (P = 0.06) | | | | | | | | |
| **Total (95% CI)** | | | **1840** | | | **1859** | **100.0%** | **-0.40 [-0.62 , -0.18]** |
| Heterogeneity: Tau² = 0.13; Chi² = 109.41, df = 14 (P < 0.00001); I² = 87% | | | | | | | | |
| Test for overall effect: Z = 3.62 (P = 0.0003) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 45.9% | | | | | | | | |




**Footnotes**

(1) At day 30, CB 0.1%, NEI grading
(2) At week 6, LE 0.5%, NEI grading
(3) At day 30, FML 0.1%, NEI grading
(4) At day 28, LE 0.25%, NEI grading
(5) At day 14, LE 0.25%, NEI grading
(6) At week 6, LE (conc. unknown)
(7) At day 21, FML 0.1%, Oxford grading scheme and Waterloo grading system
(8) At week 4, FML 0.1%; unit of analysis was eye
(9) At month 2, LE 0.5%
(10) At month 1, LE 0.1%
(11) At week 4, LE 0.5%
(12) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin, grading according to Macri and Qiu

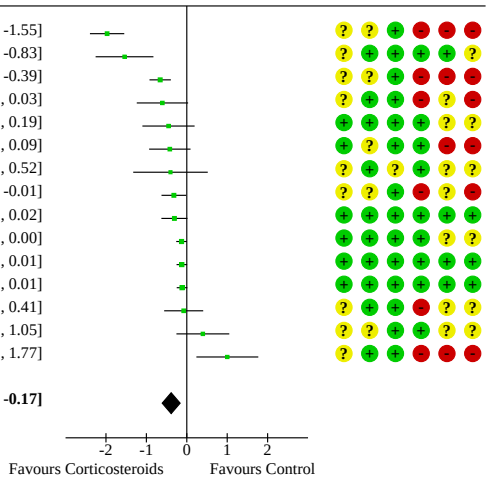
**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.15. Comparison 1: Steroids versus lubricants, Outcome 15: Corneal fluorescein staining score—Qazi: LE + tobramycin

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Cao 2018 (1) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 7.0% | -1.97 [-2.40 , -1.55] |
| Pinto-Fraga 2016 (2) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.8% | -1.54 [-2.26 , -0.83] |
| Li 2021 (3) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 8.3% | -0.66 [-0.92 , -0.39] |
| Aragona 2013 (4) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.3% | -0.60 [-1.24 , 0.03] |
| Akhlaq 2019 (5) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.2% | -0.45 [-1.10 , 0.19] |
| Lee 2014 (6) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.3% | -0.42 [-0.93 , 0.09] |
| Avunduk 2003 (7) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.6% | -0.40 [-1.33 , 0.52] |
| Chen 2020 (8) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 8.0% | -0.32 [-0.63 , -0.01] |
| KPI-121 (Phase 2) (9) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.9% | -0.31 [-0.63 , 0.02] |
| KPI-121 (STRIDE3) (10) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 9.2% | -0.13 [-0.26 , 0.00] |
| KPI-121 (STRIDE1) (10) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 9.2% | -0.12 [-0.25 , 0.01] |
| KPI-121 (STRIDE2) (10) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 9.2% | -0.12 [-0.25 , 0.01] |
| Pflugfelder 2004 (11) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.5% | -0.08 [-0.56 , 0.41] |
| Qazi 2015 (12) | 6.3 | 4.2 | 17 | 4.8 | 3.2 | 20 | 5.2% | 0.40 [-0.26 , 1.05] |
| Luo 2013 (13) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.4% | 1.00 [0.24 , 1.77] |
| **Total (95% CI)** | | | **1840** | | | **1859** | **100.0%** | **-0.39 [-0.61 , -0.17]** |

Heterogeneity: Tau² = 0.13; Chi² = 112.18, df = 14 (P < 0.00001); I² = 88%
Test for overall effect: Z = 3.42 (P = 0.0006)
Test for subgroup differences: Not applicable




**Footnotes**

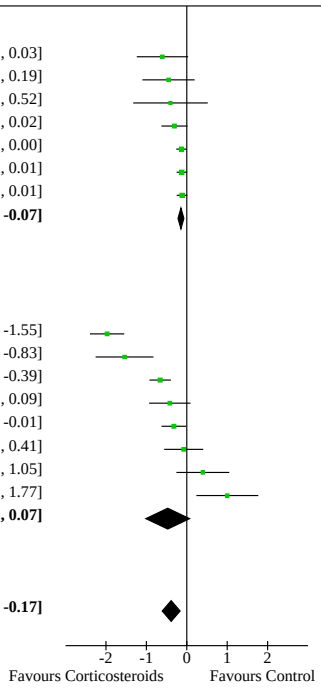
(1) At week 6, LE (conc. unknown)
(2) At day 21, FML 01%, Oxford grading scheme and Waterloo grading system
(3) At week 4, FML 0.1%, unit of analysis was eye (N=116, 232 eyes)
(4) At day 30, CB 0.1%, NEI grading
(5) At week 6, LE 0.5%, NEI grading
(6) At month 2, LE
(7) At day 30, FML, NEI grading
(8) At month 1, LE 0.1%
(9) At day 28, LE 0.25%, NEI grading
(10) At day 14, LE 0.25%, NEI grading change scores
(11) At week 4, LE 0.5%
(12) At week 4, LE 0.5% + tobramycin
(13) At week 1, dexamethasone + tobramycin vs. ATS + tobramycin, grading according to Macri and Qiu

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.16. Comparison 1: Steroids versus lubricants, Outcome 16: Corneal fluorescein staining score—by grading system, Qazi: LE + tobramycin

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|---|---|
| **1.16.1 NEI grading** | | | | | | | | | |
| Aragona 2013 (1) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.3% | -0.60 [-1.24 , 0.03] | ? + + ? + ? |
| Akhlaq 2019 (2) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.2% | -0.45 [-1.10 , 0.19] | + + + + ? ? |
| Avunduk 2003 (3) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.6% | -0.40 [-1.33 , 0.52] | ? + + + ? ? |
| KPI-121 (Phase 2) (4) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.9% | -0.31 [-0.63 , 0.02] | + + + + + + |
| KPI-121 (STRIDE3) (5) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 9.2% | -0.13 [-0.26 , 0.00] | + + + + ? ? |
| KPI-121 (STRIDE1) (5) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 9.2% | -0.12 [-0.25 , 0.01] | + + + + + + |
| KPI-121 (STRIDE2) (5) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 9.2% | -0.12 [-0.25 , 0.01] | + + + + + + |
| **Subtotal (95% CI)** | | | **1462** | | | **1478** | **49.5%** | **-0.14 [-0.22 , -0.07]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.46, df = 6 (P = 0.61); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 3.92 (P < 0.0001) | | | | | | | | | |
| **1.16.2 Other grading systems** | | | | | | | | | |
| Cao 2018 (6) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 7.0% | -1.97 [-2.40 , -1.55] | ? ? + - - - |
| Pinto-Fraga 2016 (7) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.8% | -1.54 [-2.26 , -0.83] | ? + + + + ? |
| Li 2021 (8) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 8.3% | -0.66 [-0.92 , -0.39] | ? ? + - - - |
| Lee 2014 (9) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.3% | -0.42 [-0.93 , 0.09] | + ? + + - - |
| Chen 2020 (10) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 8.0% | -0.32 [-0.63 , -0.01] | ? ? + - ? - |
| Pflugfelder 2004 (11) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.5% | -0.08 [-0.56 , 0.41] | ? + + + ? ? |
| Qazi 2015 (12) | 6.3 | 4.2 | 17 | 4.8 | 3.2 | 20 | 5.2% | 0.40 [-0.26 , 1.05] | ? + + + ? ? |
| Luo 2013 (13) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.4% | 1.00 [0.24 , 1.77] | ? + + - - - |
| **Subtotal (95% CI)** | | | **378** | | | **381** | **50.5%** | **-0.47 [-1.01 , 0.07]** | |
| Heterogeneity: Tau² = 0.54; Chi² = 80.91, df = 7 (P < 0.00001); I² = 91% | | | | | | | | | |
| Test for overall effect: Z = 1.71 (P = 0.09) | | | | | | | | | |
| **Total (95% CI)** | | | **1840** | | | **1859** | **100.0%** | **-0.39 [-0.61 , -0.17]** | |
| Heterogeneity: Tau² = 0.13; Chi² = 112.18, df = 14 (P < 0.00001); I² = 88% | | | | | | | | | |
| Test for overall effect: Z = 3.42 (P = 0.0006) | | | | | | | | | |
| Test for subgroup differences: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.3% | | | | | | | | | |




**Footnotes**

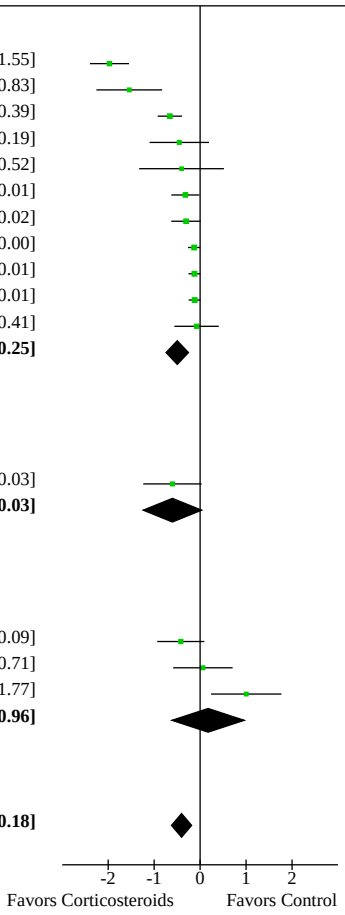
(1) At day 30, CB 0.1%, NEI grading
(2) At week 6, LE 0.5%, NEI grading
(3) At day 30, FML 0.1%, NEI grading
(4) At day 28, LE 0.25%, NEI grading
(5) At day 14, LE 0.25%, NEI grading
(6) At week 6, LE (conc. unknown)
(7) At day 21, FML 0.1%, Oxford grading scheme and Waterloo grading system
(8) At week 4, FML 0.1%; unit of analysis was eye
(9) At month 2, LE 0.5%
(10) At month 1, LE 0.1%
(11) At week 4, LE 0.5%
(12) At week 4, LE 0.5% + tobramycin
(13) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin, grading according to Macri and Qiu

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.17. Comparison 1: Steroids versus lubricants, Outcome 17: Corneal fluorescein staining scores—by etiology

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.17.1 Mixed patient population** | | | | | | | | |
| Cao 2018 (1) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 7.0% | -1.97 [-2.40 , -1.55] |
| Pinto-Fraga 2016 (2) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.7% | -1.54 [-2.26 , -0.83] |
| Li 2021 (3) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 8.4% | -0.66 [-0.92 , -0.39] |
| Akhlaq 2019 (4) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.2% | -0.45 [-1.10 , 0.19] |
| Avunduk 2003 (5) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.5% | -0.40 [-1.33 , 0.52] |
| Chen 2020 (6) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 8.0% | -0.32 [-0.63 , -0.01] |
| KPI-121 (Phase 2) (7) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.9% | -0.31 [-0.63 , 0.02] |
| KPI-121 (STRIDE3) (8) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 9.2% | -0.13 [-0.26 , 0.00] |
| KPI-121 (STRIDE1) (8) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 9.2% | -0.12 [-0.25 , 0.01] |
| KPI-121 (STRIDE2) (8) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 9.2% | -0.12 [-0.25 , 0.01] |
| Pflugfelder 2004 (9) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.5% | -0.08 [-0.56 , 0.41] |
| **Subtotal (95% CI)** | | | **1758** | | | **1774** | **78.9%** | **-0.50 [-0.74 , -0.25]** |
| Heterogeneity: Tau² = 0.13; Chi² = 96.78, df = 10 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 4.00 (P < 0.0001) | | | | | | | | |
| **1.17.2 Patients with Sjögren syndrome** | | | | | | | | |
| Aragona 2013 (10) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.3% | -0.60 [-1.24 , 0.03] |
| **Subtotal (95% CI)** | | | **20** | | | **20** | **5.3%** | **-0.60 [-1.24 , 0.03]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.86 (P = 0.06) | | | | | | | | |
| **1.17.3 Patients with Meibomian Gland Dysfunction** | | | | | | | | |
| Lee 2014 (11) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.3% | -0.42 [-0.93 , 0.09] |
| Qazi 2015 (9) | 5 | 3.3 | 17 | 4.8 | 3.2 | 20 | 5.2% | 0.06 [-0.59 , 0.71] |
| Luo 2013 (12) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.4% | 1.00 [0.24 , 1.77] |
| **Subtotal (95% CI)** | | | **62** | | | **65** | **15.8%** | **0.17 [-0.61 , 0.96]** |
| Heterogeneity: Tau² = 0.38; Chi² = 9.18, df = 2 (P = 0.01); I² = 78% | | | | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | | | | |
| **Total (95% CI)** | | | **1840** | | | **1859** | **100.0%** | **-0.40 [-0.62 , -0.18]** |
| Heterogeneity: Tau² = 0.13; Chi² = 109.41, df = 14 (P < 0.00001); I² = 87% | | | | | | | | |
| Test for overall effect: Z = 3.62 (P = 0.0003) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.77, df = 2 (P = 0.25), I² = 27.9% | | | | | | | | |

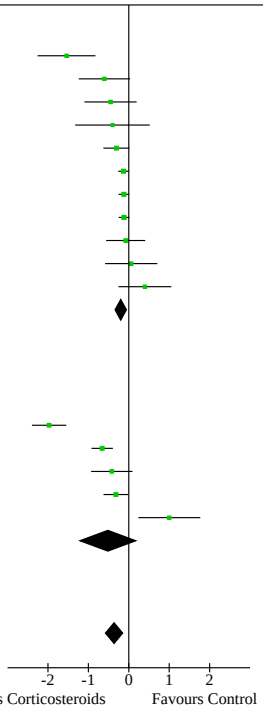


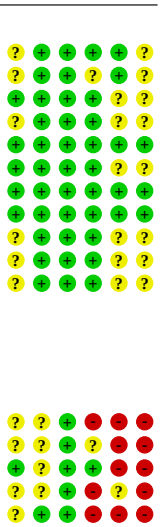

**Footnotes**

(1) At week 6, LE (conc. unknown)
(2) At day 21, FML 01%, Oxford grading scheme and Waterloo grading system
(3) At week 4, FML 0.1%, unit of analysis was eye
(4) At week 6, LE 0.5%, NEI grading
(5) At day 30, FML, NEI grading
(6) At month 1, LE 0.1%
(7) At day 28, LE 0.25%, NEI grading
(8) At day 14, LE 0.25%, NEI grading change scores
(9) At week 4, LE 0.5%
(10) At day 30, CB 0.1%, NEI grading
(11) At month 2, LE
(12) At week 1, dexamethasone + tobramycin vs. ATS + tobramycin, grading according to Macri and Qiu

# Analysis 1.18. Comparison 1: Steroids versus lubricants, Outcome 18: Corneal fluorescein staining score—by risk of bias

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.18.1 Low/some concerns RoB** | | | | | | | | |
| Pinto-Fraga 2016 (1) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.5% | -1.54 [-2.26 , -0.83] |
| Aragona 2013 (2) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.0% | -0.60 [-1.24 , 0.03] |
| Akhlaq 2019 (3) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.0% | -0.45 [-1.10 , 0.19] |
| Avunduk 2003 (2) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.4% | -0.40 [-1.33 , 0.52] |
| KPI-121 (Phase 2) (4) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.5% | -0.31 [-0.63 , 0.02] |
| KPI-121 (STRIDE3) (5) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 8.7% | -0.13 [-0.26 , 0.00] |
| KPI-121 (STRIDE1) (5) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 8.7% | -0.12 [-0.25 , 0.01] |
| KPI-121 (STRIDE2) (5) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 8.7% | -0.12 [-0.25 , 0.01] |
| Pflugfelder 2004 (6) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.2% | -0.08 [-0.56 , 0.41] |
| Qazi 2015 (6) | 5 | 3.3 | 17 | 4.8 | 3.2 | 20 | 5.0% | 0.06 [-0.59 , 0.71] |
| Qazi 2015 (6) | 6.3 | 4.2 | 17 | 4.8 | 3.2 | 20 | 4.9% | 0.40 [-0.26 , 1.05] |
| **Subtotal (95% CI)** | | | **1549** | | | **1571** | **67.6%** | **-0.20 [-0.34 , -0.06]** |
| Heterogeneity: Tau² = 0.02; Chi² = 22.19, df = 10 (P = 0.01); I² = 55% | | | | | | | | |
| Test for overall effect: Z = 2.76 (P = 0.006) | | | | | | | | |
| **1.18.2 High RoB** | | | | | | | | |
| Cao 2018 (7) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 6.7% | -1.97 [-2.40 , -1.55] |
| Li 2021 (6) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 7.9% | -0.66 [-0.92 , -0.39] |
| Lee 2014 (8) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.0% | -0.42 [-0.93 , 0.09] |
| Chen 2020 (9) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 7.6% | -0.32 [-0.63 , -0.01] |
| Luo 2013 (10) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.2% | 1.00 [0.24 , 1.77] |
| **Subtotal (95% CI)** | | | **308** | | | **308** | **32.4%** | **-0.52 [-1.21 , 0.18]** |
| Heterogeneity: Tau² = 0.57; Chi² = 60.40, df = 4 (P < 0.00001); I² = 93% | | | | | | | | |
| Test for overall effect: Z = 1.46 (P = 0.14) | | | | | | | | |
| **Total (95% CI)** | | | **1857** | | | **1879** | **100.0%** | **-0.36 [-0.58 , -0.15]** |
| Heterogeneity: Tau² = 0.13; Chi² = 112.94, df = 15 (P < 0.00001); I² = 87% | | | | | | | | |
| Test for overall effect: Z = 3.33 (P = 0.0009) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0% | | | | | | | | |



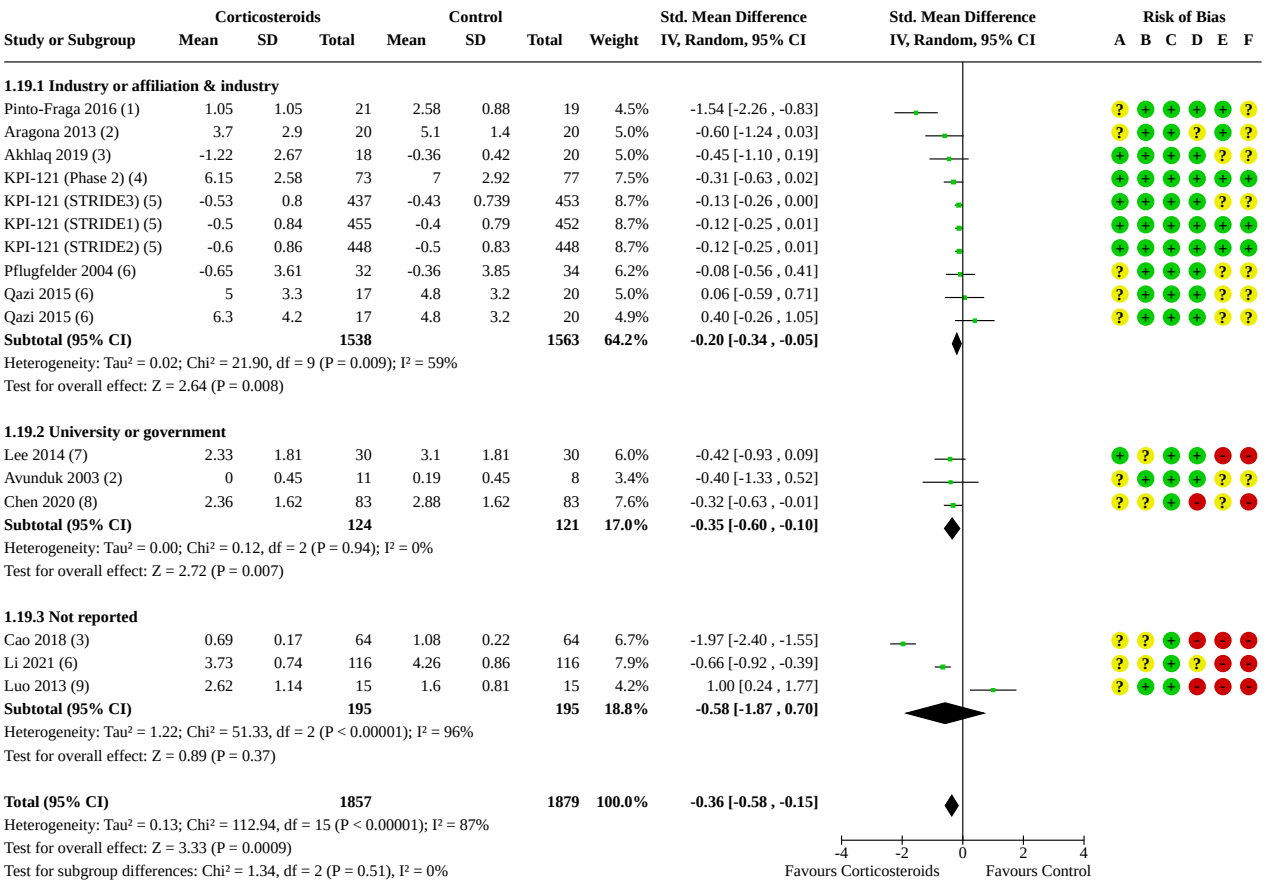

**Footnotes**

(1) At day 21, Oxford grading scheme and Waterloo grading system
(2) At day 30, NEI grading
(3) At week 6, NEI grading
(4) At day 28, NEI grading
(5) At day 14, NEI grading
(6) At week 4
(7) At week 6
(8) At month 2
(9) At month 1
(10) At week 1, grading according to Macri and Qiu

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

# Analysis 1.19. Comparison 1: Steroids versus lubricants, Outcome 19: Corneal fluorescein staining score—by sponsorship




**Footnotes**

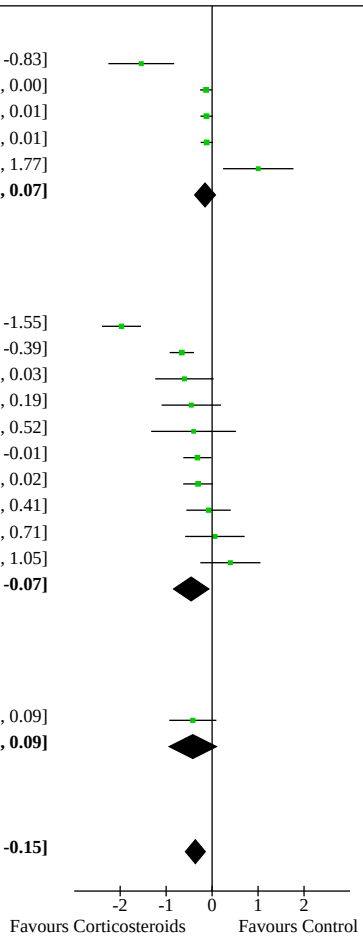
(1) At day 21
(2) At day 30
(3) At week 6
(4) At day 28
(5) At day 14
(6) At week 4
(7) At month 2
(8) At month 1
(9) At week 1

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.20. Comparison 1: Steroids versus lubricants, Outcome 20: Corneal fluorescein staining score—by steroid treatment duration

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.20.1 Short-term (< 28 days)** | | | | | | | | |
| Pinto-Fraga 2016 (1) | 1.05 | 1.05 | 21 | 2.58 | 0.88 | 19 | 4.5% | -1.54 [-2.26 , -0.83] |
| KPI-121 (STRIDE3) (2) | -0.53 | 0.8 | 437 | -0.43 | 0.739 | 453 | 8.7% | -0.13 [-0.26 , 0.00] |
| KPI-121 (STRIDE1) (2) | -0.5 | 0.84 | 455 | -0.4 | 0.79 | 452 | 8.7% | -0.12 [-0.25 , 0.01] |
| KPI-121 (STRIDE2) (2) | -0.6 | 0.86 | 448 | -0.5 | 0.83 | 448 | 8.7% | -0.12 [-0.25 , 0.01] |
| Luo 2013 (3) | 2.62 | 1.14 | 15 | 1.6 | 0.81 | 15 | 4.2% | 1.00 [0.24 , 1.77] |
| **Subtotal (95% CI)** | | | **1376** | | | **1387** | **34.9%** | **-0.15 [-0.38 , 0.07]** |
| Heterogeneity: Tau² = 0.04; Chi² = 23.41, df = 4 (P = 0.0001); I² = 83% | | | | | | | | |
| Test for overall effect: Z = 1.34 (P = 0.18) | | | | | | | | |
| **1.20.2 Short-term (28 to 42 days)** | | | | | | | | |
| Cao 2018 (4) | 0.69 | 0.17 | 64 | 1.08 | 0.22 | 64 | 6.7% | -1.97 [-2.40 , -1.55] |
| Li 2021 (5) | 3.73 | 0.74 | 116 | 4.26 | 0.86 | 116 | 7.9% | -0.66 [-0.92 , -0.39] |
| Aragona 2013 (6) | 3.7 | 2.9 | 20 | 5.1 | 1.4 | 20 | 5.0% | -0.60 [-1.24 , 0.03] |
| Akhlaq 2019 (7) | -1.22 | 2.67 | 18 | -0.36 | 0.42 | 20 | 5.0% | -0.45 [-1.10 , 0.19] |
| Avunduk 2003 (8) | 0 | 0.45 | 11 | 0.19 | 0.45 | 8 | 3.4% | -0.40 [-1.33 , 0.52] |
| Chen 2020 (9) | 2.36 | 1.62 | 83 | 2.88 | 1.62 | 83 | 7.6% | -0.32 [-0.63 , -0.01] |
| KPI-121 (Phase 2) (10) | 6.15 | 2.58 | 73 | 7 | 2.92 | 77 | 7.5% | -0.31 [-0.63 , 0.02] |
| Pflugfelder 2004 (11) | -0.65 | 3.61 | 32 | -0.36 | 3.85 | 34 | 6.2% | -0.08 [-0.56 , 0.41] |
| Qazi 2015 (11) | 5 | 3.3 | 17 | 4.8 | 3.2 | 20 | 5.0% | 0.06 [-0.59 , 0.71] |
| Qazi 2015 (12) | 6.3 | 4.2 | 17 | 4.8 | 3.2 | 20 | 4.9% | 0.40 [-0.26 , 1.05] |
| **Subtotal (95% CI)** | | | **451** | | | **462** | **59.1%** | **-0.46 [-0.84 , -0.07]** |
| Heterogeneity: Tau² = 0.30; Chi² = 63.38, df = 9 (P < 0.00001); I² = 86% | | | | | | | | |
| Test for overall effect: Z = 2.34 (P = 0.02) | | | | | | | | |
| **1.20.3 Duration ≥ 2 months** | | | | | | | | |
| Lee 2014 (13) | 2.33 | 1.81 | 30 | 3.1 | 1.81 | 30 | 6.0% | -0.42 [-0.93 , 0.09] |
| **Subtotal (95% CI)** | | | **30** | | | **30** | **6.0%** | **-0.42 [-0.93 , 0.09]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.61 (P = 0.11) | | | | | | | | |
| **Total (95% CI)** | | | **1857** | | | **1879** | **100.0%** | **-0.36 [-0.58 , -0.15]** |
| Heterogeneity: Tau² = 0.13; Chi² = 112.94, df = 15 (P < 0.00001); I² = 87% | | | | | | | | |
| Test for overall effect: Z = 3.33 (P = 0.0009) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.23, df = 2 (P = 0.33), I² = 10.4% | | | | | | | | |

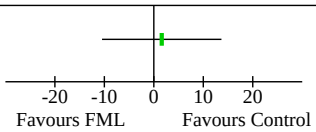



**Footnotes**

(1) At day 21, FML 0.1%
(2) At day 14, LE 0.25%
(3) At week 1, dexamethasone + tobramycin vs. artificial tears + tobramycin
(4) At week 6, LE (conc. unknown)
(5) At week 4, FML 0.1%; unit of analysis was eye
(6) At day 30, CB 0.1%
(7) At week 6, LE 0.5%
(8) At day 30, FML 0.1%
(9) At month 1, LE 0.1%
(10) At day 28, LE 0.25%
(11) At week 4, LE 0.5%
(12) At week 4, LE 0.5% + tobramycin
(13) At month 2, LE 0.5%

## Analysis 1.21. Comparison 1: Steroids versus lubricants, Outcome 21: Tear osmolarity

| Study or Subgroup | FML Mean | FML SD | FML Total | Placebo Mean | Placebo SD | Placebo Total | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Pinto-Fraga 2016 (1) | 338.5 | 15.81 | 21 | 336.9 | 22.23 | 19 | 1.60 [-10.47 , 13.67] |



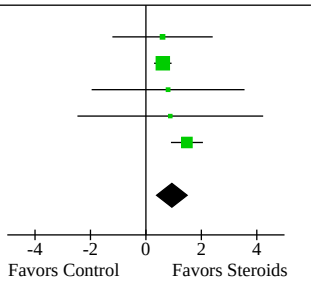

**Footnotes**

(1) At day 21, FML 0.1%, before exposing participants to adverse controlled environment

## Analysis 1.22. Comparison 1: Steroids versus lubricants, Outcome 22: Schirmer's test—Qazi: LE alone

| Study or Subgroup | Corticoseroids Mean | Corticoseroids SD | Corticoseroids Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Pinto-Fraga 2016 (1) | 5.6 | 3.21 | 21 | 5 | 2.62 | 19 | 8.0% | 0.60 [-1.21 , 2.41] |
| Li 2021 (2) | 8.43 | 1.2 | 116 | 7.82 | 1.25 | 116 | 49.7% | 0.61 [0.29 , 0.93] |
| Qazi 2015 (3) | 3.8 | 5.4 | 17 | 3 | 2.3 | 20 | 3.7% | 0.80 [-1.96 , 3.56] |
| Pflugfelder 2004 (4) | 10.91 | 5.73 | 34 | 10.03 | 7.91 | 32 | 2.6% | 0.88 [-2.47 , 4.23] |
| Chen 2020 (5) | 8.72 | 1.65 | 83 | 7.24 | 2.11 | 83 | 36.0% | 1.48 [0.90 , 2.06] |
| **Total (95% CI)** | | | **271** | | | **270** | **100.0%** | **0.94 [0.39 , 1.49]** |

Heterogeneity: Tau² = 0.13; Chi² = 6.79, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 3.34 (P = 0.0009)
Test for subgroup differences: Not applicable



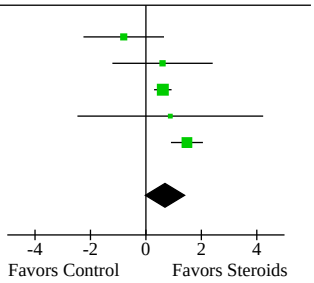

**Footnotes**

(1) At day 22, FML 0.1%
(2) At week 4, FML 0.1%; unit of analysis eye
(3) At week 4, LE 0.5%, Schirmer's test with anesthesia
(4) At week 4, LE 0.5%
(5) At month 1, LE 0.1%

## Analysis 1.23. Comparison 1: Steroids versus lubricants, Outcome 23: Schirmer's test—Qazi: LE + tobramycin

| Study or Subgroup | Corticoseroids Mean | Corticoseroids SD | Corticoseroids Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Qazi 2015 (1) | 2.2 | 2.2 | 17 | 3 | 2.3 | 20 | 15.0% | -0.80 [-2.25 , 0.65] |
| Pinto-Fraga 2016 (2) | 5.6 | 3.21 | 21 | 5 | 2.62 | 19 | 11.1% | 0.60 [-1.21 , 2.41] |
| Li 2021 (3) | 8.43 | 1.2 | 116 | 7.82 | 1.25 | 116 | 37.8% | 0.61 [0.29 , 0.93] |
| Pflugfelder 2004 (4) | 10.91 | 5.73 | 34 | 10.03 | 7.91 | 32 | 4.0% | 0.88 [-2.47 , 4.23] |
| Chen 2020 (5) | 8.72 | 1.65 | 83 | 7.24 | 2.11 | 83 | 32.1% | 1.48 [0.90 , 2.06] |
| **Total (95% CI)** | | | **271** | | | **270** | **100.0%** | **0.69 [-0.02 , 1.39]** |

Heterogeneity: Tau² = 0.32; Chi² = 11.33, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable

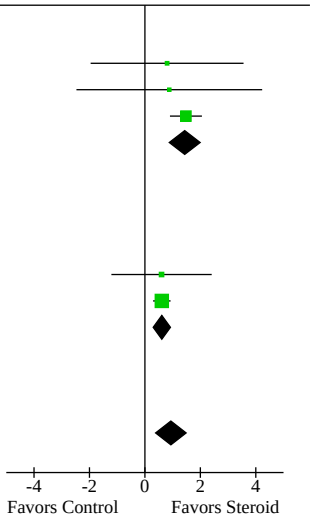



**Footnotes**

(1) At week 4, LE 0.5% + tobramycin 0.3%, Schirmer's test with anesthesia
(2) At day 22, FML 0.1%
(3) At week 4, FML 0.1%; unit of analysis eye
(4) At week 4, LE 0.5%
(5) At month 1, LE 0.1%

## Analysis 1.24. Comparison 1: Steroids versus lubricants, Outcome 24: Schirmer test—by steroid type, Qazi: LE alone

| Study or Subgroup | Corticoseroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.24.1 Loteprednol etabonate (LE): Ketone steroid** | | | | | | | | |
| Qazi 2015 (1) | 3.8 | 5.4 | 17 | 3 | 2.3 | 20 | 3.7% | 0.80 [-1.96 , 3.56] |
| Pflugfelder 2004 (2) | 10.91 | 5.73 | 34 | 10.03 | 7.91 | 32 | 2.6% | 0.88 [-2.47 , 4.23] |
| Chen 2020 (3) | 8.72 | 1.65 | 83 | 7.24 | 2.11 | 83 | 36.0% | 1.48 [0.90 , 2.06] |
| **Subtotal (95% CI)** | | | **134** | | | **135** | **42.3%** | **1.44 [0.88 , 1.99]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 5.06 (P < 0.00001) | | | | | | | | |
| **1.24.2 Fluorometholone (FML): Ester steroid** | | | | | | | | |
| Pinto-Fraga 2016 (4) | 5.6 | 3.21 | 21 | 5 | 2.62 | 19 | 8.0% | 0.60 [-1.21 , 2.41] |
| Li 2021 (5) | 8.43 | 1.2 | 116 | 7.82 | 1.25 | 116 | 49.7% | 0.61 [0.29 , 0.93] |
| **Subtotal (95% CI)** | | | **137** | | | **135** | **57.7%** | **0.61 [0.30 , 0.92]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.85 (P = 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **271** | | | **270** | **100.0%** | **0.94 [0.39 , 1.49]** |
| Heterogeneity: Tau² = 0.13; Chi² = 6.79, df = 4 (P = 0.15); I² = 41% | | | | | | | | |
| Test for overall effect: Z = 3.34 (P = 0.0009) | | | | | | | | |
| Test for subgroup differences: Chi² = 6.46, df = 1 (P = 0.01), I² = 84.5% | | | | | | | | |

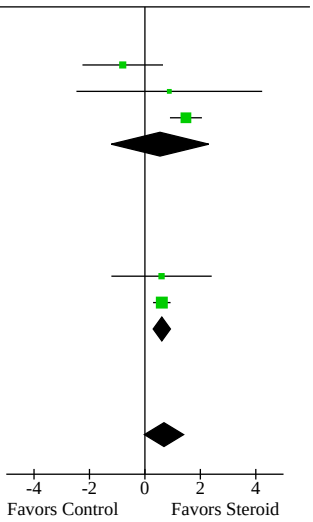



**Footnotes**

(1) At week 4, LE 0.5%, Schirmer's test with anesthesia
(2) At week 4, LE 0.5%
(3) At month 1, LE 0.1%
(4) At day 22, FML 0.1%
(5) At week 4, FML 0.1%; unit of analysis was eye

## Analysis 1.25. Comparison 1: Steroids versus lubricants, Outcome 25: Schirmer test—by steroid type, Qazi: LE + tobramycin

| Study or Subgroup | Corticoseroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.25.1 Loteprednol etabonate (LE): Ketone steroid** | | | | | | | | |
| Qazi 2015 (1) | 2.2 | 2.2 | 17 | 3 | 2.3 | 20 | 15.0% | -0.80 [-2.25 , 0.65] |
| Pflugfelder 2004 (2) | 10.91 | 5.73 | 34 | 10.03 | 7.91 | 32 | 4.0% | 0.88 [-2.47 , 4.23] |
| Chen 2020 (3) | 8.72 | 1.65 | 83 | 7.24 | 2.11 | 83 | 32.1% | 1.48 [0.90 , 2.06] |
| **Subtotal (95% CI)** | | | **134** | | | **135** | **51.1%** | **0.54 [-1.21 , 2.30]** |
| Heterogeneity: Tau² = 1.66; Chi² = 8.21, df = 2 (P = 0.02); I² = 76% | | | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | | | |
| **1.25.2 Fluorometholone (FML): Ester steroid** | | | | | | | | |
| Pinto-Fraga 2016 (4) | 5.6 | 3.21 | 21 | 5 | 2.62 | 19 | 11.1% | 0.60 [-1.21 , 2.41] |
| Li 2021 (5) | 8.43 | 1.2 | 116 | 7.82 | 1.25 | 116 | 37.8% | 0.61 [0.29 , 0.93] |
| **Subtotal (95% CI)** | | | **137** | | | **135** | **48.9%** | **0.61 [0.30 , 0.92]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.85 (P = 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **271** | | | **270** | **100.0%** | **0.69 [-0.02 , 1.39]** |
| Heterogeneity: Tau² = 0.32; Chi² = 11.33, df = 4 (P = 0.02); I² = 65% | | | | | | | | |
| Test for overall effect: Z = 1.91 (P = 0.06) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0% | | | | | | | | |

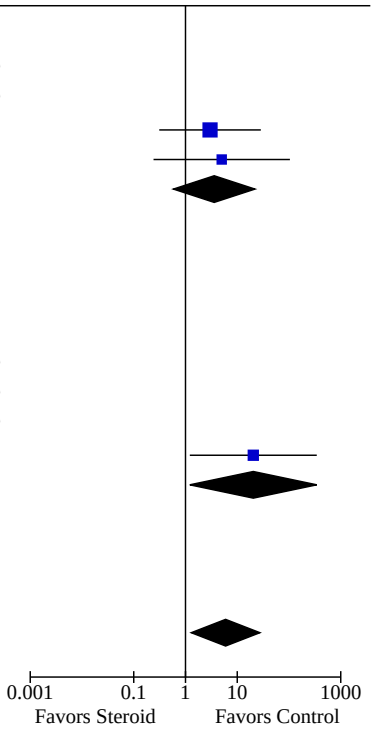



**Footnotes**

(1) At week 4, LE 0.5% + tobramycin 0.3%, Schirmer's test with anesthesia
(2) At week 4, LE 0.5%
(3) At month 1, LE 0.1%
(4) At day 22, FML 0.1%
(5) At week 4, FML 0.1%; unit of analysis was eye

## Analysis 1.26. Comparison 1: Steroids versus lubricants, Outcome 26: Proportion of participants with increased IOP—by steroid type

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.26.1 Ester steroid: LE** | | | | | | |
| Pflugfelder 2004 (1) | 0 | 32 | 0 | 34 | | Not estimable |
| Lee 2014 (2) | 0 | 36 | 0 | 32 | | Not estimable |
| KPI-121 (STRIDE1) (3) | 3 | 459 | 1 | 456 | 45.6% | 2.98 [0.31 , 28.55] |
| KPI-121 (STRIDE2) (3) | 2 | 452 | 0 | 453 | 25.3% | 5.01 [0.24 , 104.09] |
| **Subtotal (95% CI)** | | **979** | | **975** | **70.8%** | **3.59 [0.59 , 21.97]** |
| Total events: | 5 | | 1 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | | |
| **1.26.2 Ketone steroids** | | | | | | |
| Avunduk 2003 (4) | 0 | 11 | 0 | 8 | | Not estimable |
| Aragona 2013 (5) | 0 | 20 | 0 | 20 | | Not estimable |
| Pinto-Fraga 2016 (6) | 0 | 21 | 0 | 19 | | Not estimable |
| NCT01276223 (7) | 10 | 107 | 0 | 104 | 29.2% | 20.42 [1.21 , 344.00] |
| **Subtotal (95% CI)** | | **159** | | **151** | **29.2%** | **20.42 [1.21 , 344.00]** |
| Total events: | 10 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.09 (P = 0.04) | | | | | | |
| **Total (95% CI)** | | **1138** | | **1126** | **100.0%** | **5.96 [1.30 , 27.38]** |
| Total events: | 15 | | 1 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 2 (P = 0.54); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.29 (P = 0.02) | | | | | | |
| Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 3.1% | | | | | | |

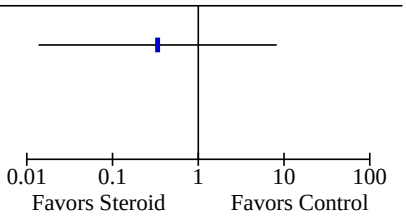



**Footnotes**

(1) LE 0.5% for 4 weeks
(2) LE 0.5% for 2 months
(3) LE 0.25% for 14 days
(4) FML 0.1% for 30 days
(5) CB 0.1% for 30 days
(6) FML 0.1% for 21 days
(7) Difluprednate 0.05% for 4 weeks

### Analysis 1.27. Comparison 1: Steroids versus lubricants, Outcome 27: Proportion of participants with new cataract formation

| Study or Subgroup | Steroid Events | Steroid Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| KPI-121 (STRIDE3) (1) | 0 | 449 | 1 | 452 | 0.34 [0.01 , 8.22] |
| Pflugfelder 2004 (2) | 0 | 128 | 0 | 136 | Not estimable |
| Pinto-Fraga 2016 (3) | 0 | 21 | 0 | 19 | Not estimable |



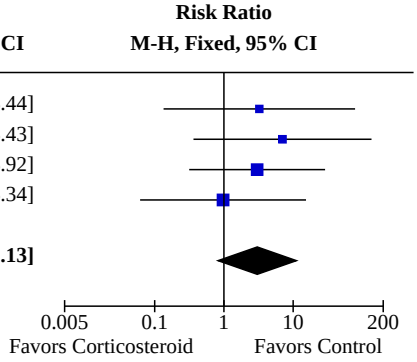

**Footnotes**

(1) LE 0.25% for 14 days
(2) LE 0.5% for 4 weeks
(3) FML 0.1% for 21 days

### Analysis 1.28. Comparison 1: Steroids versus lubricants, Outcome 28: Proportion of participants with serious adverse events (systemic or ocular)

| Study or Subgroup | Corticosteroid Events | Corticosteroid Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| KPI-121 (Phase 2) (1) | 1 | 72 | 0 | 78 | 16.1% | 3.25 [0.13 , 78.44] |
| KPI-121 (STRIDE2) (2) | 3 | 452 | 0 | 453 | 16.7% | 7.02 [0.36 , 135.43] |
| KPI-121 (STRIDE3) (2) | 3 | 449 | 1 | 452 | 33.3% | 3.02 [0.32 , 28.92] |
| NCT01276223 (3) | 1 | 107 | 1 | 104 | 33.9% | 0.97 [0.06 , 15.34] |
| **Total (95% CI)** | | **1080** | | **1087** | **100.0%** | **3.03 [0.82 , 11.13]** |
| Total events: | 8 | | 2 | | | |

Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable




**Footnotes**

(1) LE 0.25% for 28 days
(2) LE 0.25% for 14 days
(3) Difluprednate 0.05% for 4 weeks

## Comparison 2. Steroids versus CsA

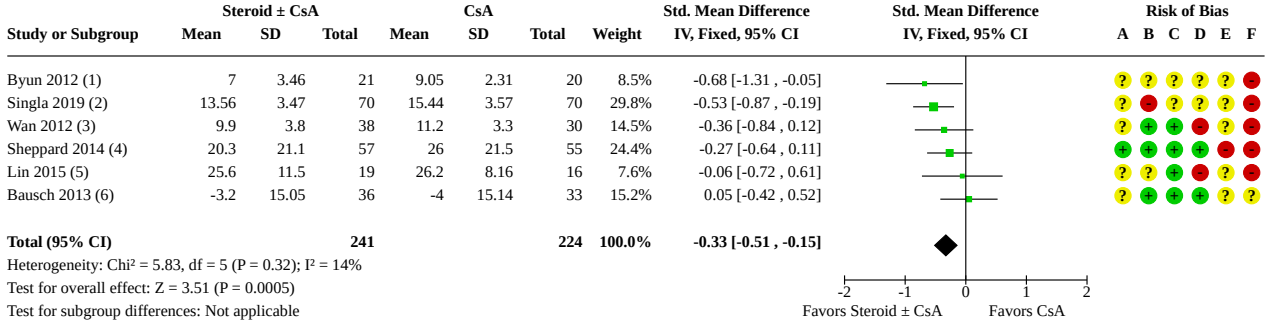
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Patient-reported symptom scores—Bausch: LE alone | 6 | 465 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.33 [-0.51, -0.15] |
| 2.2 Patient-reported symptom scores—Bausch: LE + CsA | 6 | 462 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.35 [-0.54, -0.17] |
| 2.3 Patient-reported symptom scores—by regimen | 6 | 531 | Std. Mean Difference (IV, Random, 95% CI) | -0.30 [-0.48, -0.12] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.3.1 Steroid alone vs. CsA 0.05% | 3 | 172 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.43, 0.17] |
| 2.3.2 Steroid run-in before initiating CsA 0.05% | 2 | 178 | Std. Mean Difference (IV, Random, 95% CI) | -0.21 [-0.50, 0.09] |
| 2.3.3 Steroid run-in with CsA 0.05% | 2 | 181 | Std. Mean Difference (IV, Random, 95% CI) | -0.56 [-0.86, -0.27] |
| 2.4 Patient-reported symptom scores—steroid treatment duration | 6 | 530 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.26 [-0.43, -0.08] |
| 2.4.1 High dose for 3-4 weeks before tapering | 2 | 106 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.09 [-0.47, 0.30] |
| 2.4.2 8 weeks | 4 | 355 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.37 [-0.58, -0.16] |
| 2.4.3 12 weeks | 1 | 69 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.05 [-0.42, 0.52] |
| 2.5 Tear film break-up time—Bausch: LE alone | 5 | 353 | Mean Difference (IV, Random, 95% CI) | 0.37 [-0.13, 0.87] |
| 2.6 Tear film break-up time—Bausch: LE + CsA | 5 | 350 | Mean Difference (IV, Random, 95% CI) | 0.36 [-0.15, 0.87] |
| 2.7 Tear film break-up time—by regimen | 5 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.7.1 Steroid alone | 3 | 172 | Mean Difference (IV, Random, 95% CI) | 0.28 [-0.74, 1.30] |
| 2.7.2 Steroid + CsA | 3 | 247 | Mean Difference (IV, Random, 95% CI) | 0.46 [0.16, 0.76] |
| 2.8 Tear film break-up time—by steroid treatment duration | 5 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.8.1 High dose for 2-4 weeks before tapering | 1 | 66 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.86, 1.04] |
| 2.8.2 Fixed dose for 8 weeks | 2 | 103 | Mean Difference (IV, Random, 95% CI) | 0.32 [-1.20, 1.84] |
| 2.8.3 Fixed dose for 3 months | 3 | 250 | Mean Difference (IV, Random, 95% CI) | 0.47 [0.17, 0.77] |
| 2.9 Corneal fluorescein staining scores—Bausch: LE alone | 6 | 465 | Std. Mean Difference (IV, Random, 95% CI) | 0.05 [-0.25, 0.35] |
| 2.10 Corneal fluorescein staining score—Bausch: LE + CsA | 6 | 462 | Std. Mean Difference (IV, Random, 95% CI) | 0.01 [-0.27, 0.29] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.11 Corneal fluorescein staining score—by grading system | 6 | 531 | Std. Mean Difference (IV, Random, 95% CI) | 0.05 [-0.20, 0.31] |
| 2.11.1 NEI grading system | 4 | 428 | Std. Mean Difference (IV, Random, 95% CI) | 0.01 [-0.31, 0.32] |
| 2.11.2 Other grading system | 2 | 103 | Std. Mean Difference (IV, Random, 95% CI) | 0.20 [-0.22, 0.62] |
| 2.12 Corneal fluorescein staining score—by regimen | 6 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.12.1 Steroid alone vs. CsA 0.05% | 3 | 172 | Std. Mean Difference (IV, Random, 95% CI) | 0.25 [-0.06, 0.55] |
| 2.12.2 Steroid run-in before initiating CsA 0.05% | 2 | 178 | Std. Mean Difference (IV, Random, 95% CI) | 0.16 [-0.14, 0.45] |
| 2.12.3 Steroid run-in concurrently with CsA 0.05% | 2 | 181 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-0.73, 0.07] |
| 2.13 Corneal fluorescein staining score—by steroid treatment duration | 6 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.13.1 For 3-4 weeks | 2 | 107 | Std. Mean Difference (IV, Random, 95% CI) | 0.06 [-0.32, 0.44] |
| 2.13.2 For 8 weeks | 4 | 355 | Std. Mean Difference (IV, Random, 95% CI) | 0.01 [-0.39, 0.42] |
| 2.13.3 For 12 weeks | 1 | 69 | Std. Mean Difference (IV, Random, 95% CI) | 0.32 [-0.15, 0.80] |
| 2.14 Tear osmolarity | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2.14.1 LE gel 0.5% alone | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2.14.2 LE gel 0.5% plus CsA | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2.15 Schirmer's test | 4 | 361 | Mean Difference (IV, Random, 95% CI) | 1.19 [-0.40, 2.77] |
| 2.15.1 Steroid alone | 1 | 68 | Mean Difference (IV, Random, 95% CI) | 0.12 [-0.59, 0.83] |
| 2.15.2 Combination | 3 | 293 | Mean Difference (IV, Random, 95% CI) | 1.73 [0.32, 3.13] |
| 2.16 Schirmer's test—by steroid type | 4 | 361 | Mean Difference (IV, Random, 95% CI) | 1.19 [-0.40, 2.77] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.16.1 Ketone steroid: MP + CsA | 1 | 41 | Mean Difference (IV, Random, 95% CI) | 0.80 [-0.52, 2.12] |
| 2.16.2 Ester steroid: LE ± CsA | 3 | 320 | Mean Difference (IV, Random, 95% CI) | 1.32 [-0.72, 3.36] |
| 2.17 Proportion of participants with increased IOP | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.18 Proportion of participants with any ocular complication | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.18.1 Steroid alone | 2 | 103 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.11, 3.43] |
| 2.18.2 Steroid plus CsA | 2 | 110 | Risk Ratio (M-H, Random, 95% CI) | 0.65 [0.11, 3.80] |

## Analysis 2.1. Comparison 2: Steroids versus CsA, Outcome 1: Patient-reported symptom scores—Bausch: LE alone




**Footnotes**

(1) At month 3, MP 1% + CsA
(2) At month 3, OSDI; LE 0.5% + CsA
(3) At week 8, LE 0.5% alone
(4) At day 60, OSDI; LE 0.5% four times per day for 2 weeks, concurrent LE + CsA twice per day for the rest of the study
(5) At week 8, OSDI; FML 0.1% alone
(6) At week 12, OSDI; LE gel 0.5% alone

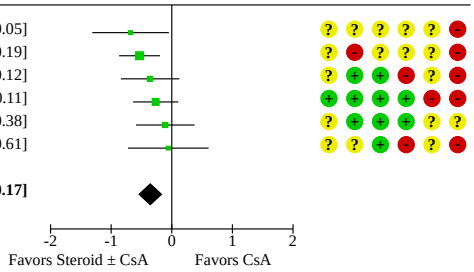
**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.2. Comparison 2: Steroids versus CsA, Outcome 2: Patient-reported symptom scores—Bausch: LE + CsA

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | CsA Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Byun 2012 (1) | 7 | 3.46 | 21 | 9.05 | 2.31 | 20 | 8.5% | -0.68 [-1.31 , -0.05] |
| Singla 2019 (2) | 13.56 | 3.47 | 70 | 15.44 | 3.57 | 70 | 29.9% | -0.53 [-0.87 , -0.19] |
| Wan 2012 (3) | 9.9 | 3.8 | 38 | 11.2 | 3.3 | 30 | 14.6% | -0.36 [-0.84 , 0.12] |
| Sheppard 2014 (4) | 20.3 | 21.1 | 57 | 26 | 21.5 | 55 | 24.6% | -0.27 [-0.64 , 0.11] |
| Bausch 2013 (5) | -5.6 | 14.5 | 33 | -4 | 15.14 | 33 | 14.6% | -0.11 [-0.59 , 0.38] |
| Lin 2015 (6) | 25.6 | 11.5 | 19 | 26.2 | 8.16 | 16 | 7.7% | -0.06 [-0.72 , 0.61] |
| **Total (95% CI)** | | | **238** | | | **224** | **100.0%** | **-0.35 [-0.54 , -0.17]** |

Heterogeneity: Chi² = 4.07, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)
Test for subgroup differences: Not applicable







**Footnotes**

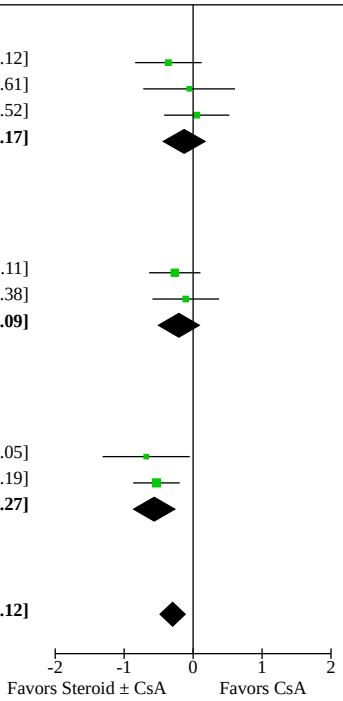
(1) At month 3, MP 1% + CsA
(2) At month 3, OSDI; LE 0.5% + CsA
(3) At week 8, LE 0.5% alone
(4) At day 60, OSDI; LE 0.5% four times per day for 2 weeks, concurrent LE + CsA twice per day for the rest of the study
(5) At week 12, OSDI; LE gel 0.5% twice per day for 2 weeks, concurrent LE + CsA twice per day for 2 weeks, then CsA alone for 8 weeks
(6) At week 8, OSDI; FML 0.1% alone

**Risk of bias legend**

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.3. Comparison 2: Steroids versus CsA, Outcome 3: Patient-reported symptom scores—by regimen

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | CsA Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.3.1 Steroid alone vs. CsA 0.05%** | | | | | | | | |
| Wan 2012 (1) | 9.9 | 3.8 | 38 | 11.2 | 3.3 | 30 | 13.0% | -0.36 [-0.84 , 0.12] |
| Lin 2015 (2) | 25.6 | 11.5 | 19 | 26.2 | 8.16 | 16 | 7.1% | -0.06 [-0.72 , 0.61] |
| Bausch 2013 (3) | -3.2 | 15.05 | 36 | -4 | 15.14 | 33 | 13.5% | 0.05 [-0.42 , 0.52] |
| **Subtotal (95% CI)** | | | **93** | | | **79** | **33.7%** | **-0.13 [-0.43 , 0.17]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 2 (P = 0.48); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.85 (P = 0.40) | | | | | | | | |
| **2.3.2 Steroid run-in before initiating CsA 0.05%** | | | | | | | | |
| Sheppard 2014 (4) | 20.3 | 21.1 | 57 | 26 | 21.5 | 55 | 20.8% | -0.27 [-0.64 , 0.11] |
| Bausch 2013 (5) | -5.6 | 14.5 | 33 | -4 | 15.14 | 33 | 13.0% | -0.11 [-0.59 , 0.38] |
| **Subtotal (95% CI)** | | | **90** | | | **88** | **33.8%** | **-0.21 [-0.50 , 0.09]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | | | | | |
| **2.3.3 Steroid run-in with CsA 0.05%** | | | | | | | | |
| Byun 2012 (6) | 7 | 3.46 | 21 | 9.05 | 2.31 | 20 | 7.9% | -0.68 [-1.31 , -0.05] |
| Singla 2019 (7) | 13.56 | 3.47 | 70 | 15.44 | 3.57 | 70 | 24.7% | -0.53 [-0.87 , -0.19] |
| **Subtotal (95% CI)** | | | **91** | | | **90** | **32.5%** | **-0.56 [-0.86 , -0.27]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.72 (P = 0.0002) | | | | | | | | |
| **Total (95% CI)** | | | **274** | | | **257** | **100.0%** | **-0.30 [-0.48 , -0.12]** |
| Heterogeneity: Tau² = 0.01; Chi² = 6.54, df = 6 (P = 0.36); I² = 8% | | | | | | | | |
| Test for overall effect: Z = 3.21 (P = 0.001) | | | | | | | | |
| Test for subgroup differences: Chi² = 4.64, df = 2 (P = 0.10), I² = 56.9% | | | | | | | | |

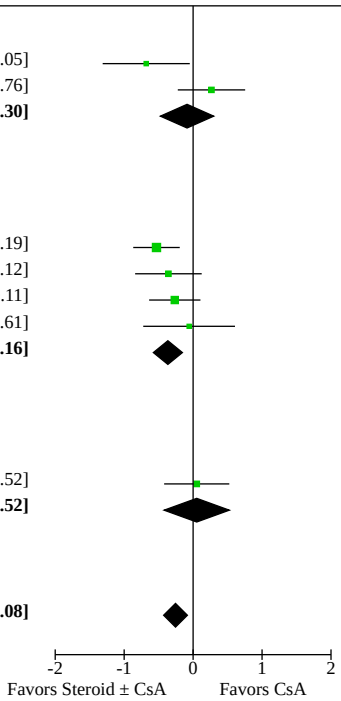



**Footnotes**

(1) At week 8, LE 0.5%
(2) At week 8, FML 0.1%
(3) At week 12, OSDI; LE gel 0.5%
(4) At day 60, LE 0.5% four times per day for 2 weeks followed by concurrent use of CsA, twice per day for both treatment, for the rest of the study
(5) At week 12, OSDI; LE gel 0.5% twice per day for 2 weeks followed by concurrent use of CsA, twice per day for both treatment, for another 2 weeks
(6) At month 3, MP 1% for 3 weeks before tapering off
(7) At month 3, LE 0.5% for up to 8 weeks

## Analysis 2.4. Comparison 2: Steroids versus CsA, Outcome 4: Patient-reported symptom scores—steroid treatment duration

| Study or Subgroup | Steroid-based Mean | SD | Total | CsA Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.4.1 High dose for 3-4 weeks before tapering** | | | | | | | | |
| Byun 2012 (1) | 7 | 3.46 | 21 | 9.05 | 2.31 | 20 | 7.4% | -0.68 [-1.31 , -0.05] |
| Bausch 2013 (2) | 0 | 14.5 | 32 | -4 | 15.14 | 33 | 12.4% | 0.27 [-0.22 , 0.76] |
| **Subtotal (95% CI)** | | | **53** | | | **53** | **19.8%** | **-0.09 [-0.47 , 0.30]** |
| Heterogeneity: Chi² = 5.40, df = 1 (P = 0.02); I² = 81% | | | | | | | | |
| Test for overall effect: Z = 0.45 (P = 0.66) | | | | | | | | |
| **2.4.2 8 weeks** | | | | | | | | |
| Singla 2019 (3) | 13.56 | 3.47 | 70 | 15.44 | 3.57 | 70 | 26.1% | -0.53 [-0.87 , -0.19] |
| Wan 2012 (4) | 9.9 | 3.8 | 38 | 11.2 | 3.3 | 30 | 12.7% | -0.36 [-0.84 , 0.12] |
| Sheppard 2014 (5) | 20.3 | 21.1 | 57 | 26 | 21.5 | 55 | 21.4% | -0.27 [-0.64 , 0.11] |
| Lin 2015 (6) | 25.6 | 11.5 | 19 | 26.2 | 8.16 | 16 | 6.7% | -0.06 [-0.72 , 0.61] |
| **Subtotal (95% CI)** | | | **184** | | | **171** | **66.9%** | **-0.37 [-0.58 , -0.16]** |
| Heterogeneity: Chi² = 2.02, df = 3 (P = 0.57); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.41 (P = 0.0007) | | | | | | | | |
| **2.4.3 12 weeks** | | | | | | | | |
| Bausch 2013 (7) | -3.2 | 15.05 | 36 | -4 | 15.14 | 33 | 13.3% | 0.05 [-0.42 , 0.52] |
| **Subtotal (95% CI)** | | | **36** | | | **33** | **13.3%** | **0.05 [-0.42 , 0.52]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.83) | | | | | | | | |
| **Total (95% CI)** | | | **273** | | | **257** | **100.0%** | **-0.26 [-0.43 , -0.08]** |
| Heterogeneity: Chi² = 10.83, df = 6 (P = 0.09); I² = 45% | | | | | | | | |
| Test for overall effect: Z = 2.91 (P = 0.004) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.41, df = 2 (P = 0.18), I² = 41.4% | | | | | | | | |

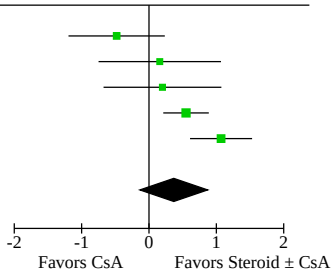



**Footnotes**

(1) At month 3, MP 1% + CsA for 3 weeks before tapering
(2) At week 12, LE 0.5% for 2 weeks, adding CsA for concurrent use for another 2 weeks, followed by CsA alone for 8 weeks
(3) At month 3, LE 0.5% four times a day for two weeks and then twice per day for another 6 weeks; CsA used for 3 months
(4) At week 8, LE 0.5% for 8 weeks
(5) At day 60, LE 0.5% four times per day for 2 weeks followed by concurrent use of CsA twice per day for the rest of the study
(6) At week 8, FML 0.1% for 8 weeks
(7) At week 12, LE 0.5% for 12 weeks

## Analysis 2.5. Comparison 2: Steroids versus CsA, Outcome 5: Tear film break-up time—Bausch: LE alone

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wan 2012 (1) | 8.45 | 1.57 | 38 | 8.93 | 1.43 | 30 | 18.7% | -0.48 [-1.19 , 0.23] |
| Bausch 2013 (2) | 0.32 | 2.04 | 36 | 0.16 | 1.81 | 33 | 15.2% | 0.16 [-0.75 , 1.07] |
| Byun 2012 (3) | 7.3 | 1.56 | 21 | 7.1 | 1.29 | 20 | 15.7% | 0.20 [-0.67 , 1.07] |
| Singla 2019 (4) | 8.86 | 1.01 | 70 | 8.31 | 1.03 | 70 | 26.4% | 0.55 [0.21 , 0.89] |
| Lin 2015 (5) | 2.68 | 0.75 | 19 | 1.61 | 0.64 | 16 | 24.0% | 1.07 [0.61 , 1.53] |
| **Total (95% CI)** | | | **184** | | | **169** | **100.0%** | **0.37 [-0.13 , 0.87]** |
| Heterogeneity: Tau² = 0.22; Chi² = 14.14, df = 4 (P = 0.007); I² = 72% | | | | | | | | |
| Test for overall effect: Z = 1.43 (P = 0.15) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



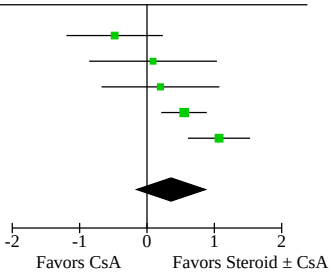

**Footnotes**

(1) At week 8, LE 0.5%
(2) At week 12, LE 0.5% gel
(3) At month 3, MP 1% + CsA
(4) At month 3, LE 0.5% + CsA
(5) At week 8, FML 0.1%

## Analysis 2.6. Comparison 2: Steroids versus CsA, Outcome 6: Tear film break-up time—Bausch: LE + CsA

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wan 2012 (1) | 8.45 | 1.57 | 38 | 8.93 | 1.43 | 30 | 18.8% | -0.48 [-1.19 , 0.23] |
| Bausch 2013 (2) | 0.25 | 2.11 | 33 | 0.16 | 1.81 | 33 | 14.7% | 0.09 [-0.86 , 1.04] |
| Byun 2012 (3) | 7.3 | 1.56 | 21 | 7.1 | 1.29 | 20 | 15.9% | 0.20 [-0.67 , 1.07] |
| Singla 2019 (4) | 8.86 | 1.01 | 70 | 8.31 | 1.03 | 70 | 26.5% | 0.55 [0.21 , 0.89] |
| Lin 2015 (5) | 2.68 | 0.75 | 19 | 1.61 | 0.64 | 16 | 24.1% | 1.07 [0.61 , 1.53] |
| **Total (95% CI)** | | | **181** | | | **169** | **100.0%** | **0.36 [-0.15 , 0.87]** |

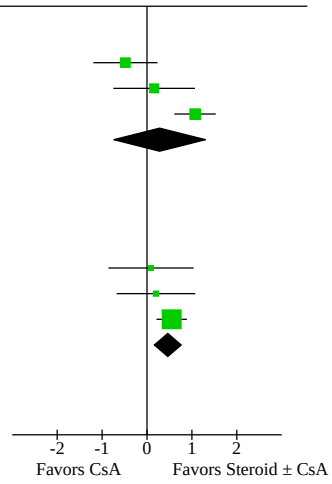
Heterogeneity: Tau² = 0.23; Chi² = 14.33, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable




**Footnotes**
(1) At week 8, LE 0.5%
(2) At week 12, LE 0.5% gel + CsA
(3) At month 3, MP 1% + CsA
(4) At month 3, LE 0.5% + CsA
(5) At week 8, FML 0.1%

## Analysis 2.7. Comparison 2: Steroids versus CsA, Outcome 7: Tear film break-up time—by regimen

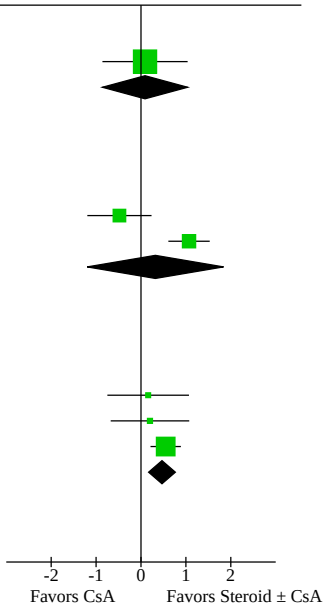
| Study or Subgroup | Steroid ± CsA Mean | SD | Total | CsA Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.7.1 Steroid alone** | | | | | | | | |
| Wan 2012 (1) | 8.45 | 1.57 | 38 | 8.93 | 1.43 | 30 | 33.2% | -0.48 [-1.19 , 0.23] |
| Bausch 2013 (2) | 0.32 | 2.04 | 36 | 0.16 | 1.81 | 33 | 30.2% | 0.16 [-0.75 , 1.07] |
| Lin 2015 (3) | 2.68 | 0.75 | 19 | 1.61 | 0.64 | 16 | 36.7% | 1.07 [0.61 , 1.53] |
| **Subtotal (95% CI)** | | | **93** | | | **79** | **100.0%** | **0.28 [-0.74 , 1.30]** |
| Heterogeneity: Tau² = 0.69; Chi² = 13.58, df = 2 (P = 0.001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | | | |
| **2.7.2 Steroid + CsA** | | | | | | | | |
| Bausch 2013 (4) | 0.25 | 2.11 | 33 | 0.16 | 1.81 | 33 | 9.9% | 0.09 [-0.86 , 1.04] |
| Byun 2012 (5) | 7.3 | 1.56 | 21 | 7.1 | 1.29 | 20 | 11.7% | 0.20 [-0.67 , 1.07] |
| Singla 2019 (6) | 8.86 | 1.01 | 70 | 8.31 | 1.03 | 70 | 78.4% | 0.55 [0.21 , 0.89] |
| **Subtotal (95% CI)** | | | **124** | | | **123** | **100.0%** | **0.46 [0.16 , 0.76]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.04 (P = 0.002) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0% | | | | | | | | |




**Footnotes**
(1) At week 8, LE 0.5%
(2) At week 12, LE 0.5% gel
(3) At week 8, FML 0.1%
(4) At week 12, LE 0.5% gel + CsA
(5) At month 3, MP 1% + CsA
(6) At month 3, LE 0.5% + CsA

## Analysis 2.8. Comparison 2: Steroids versus CsA, Outcome 8: Tear film break-up time—by steroid treatment duration

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | CsA Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.8.1 High dose for 2-4 weeks before tapering** | | | | | | | | |
| Bausch 2013 (1) | 0.25 | 2.11 | 33 | 0.16 | 1.81 | 33 | 100.0% | 0.09 [-0.86 , 1.04] |
| **Subtotal (95% CI)** | | | **33** | | | **33** | **100.0%** | **0.09 [-0.86 , 1.04]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | | | |
| **2.8.2 Fixed dose for 8 weeks** | | | | | | | | |
| Wan 2012 (2) | 8.45 | 1.57 | 38 | 8.93 | 1.43 | 30 | 48.4% | -0.48 [-1.19 , 0.23] |
| Lin 2015 (3) | 2.68 | 0.75 | 19 | 1.61 | 0.64 | 16 | 51.6% | 1.07 [0.61 , 1.53] |
| **Subtotal (95% CI)** | | | **57** | | | **46** | **100.0%** | **0.32 [-1.20 , 1.84]** |
| Heterogeneity: Tau² = 1.11; Chi² = 12.76, df = 1 (P = 0.0004); I² = 92% | | | | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | | | | | |
| **2.8.3 Fixed dose for 3 months** | | | | | | | | |
| Bausch 2013 (4) | 0.32 | 2.04 | 36 | 0.16 | 1.81 | 33 | 10.7% | 0.16 [-0.75 , 1.07] |
| Byun 2012 (5) | 7.3 | 1.56 | 21 | 7.1 | 1.29 | 20 | 11.6% | 0.20 [-0.67 , 1.07] |
| Singla 2019 (6) | 8.86 | 1.01 | 70 | 8.31 | 1.03 | 70 | 77.7% | 0.55 [0.21 , 0.89] |
| **Subtotal (95% CI)** | | | **127** | | | **123** | **100.0%** | **0.47 [0.17 , 0.77]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.08 (P = 0.002) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.57, df = 2 (P = 0.75), I² = 0% | | | | | | | | |



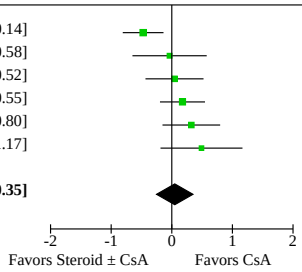

**Footnotes**

(1) At week 12, LE 0.5% gel for 2 weeks before adding CsA for 10 weeks
(2) At week 8, LE 0.5%
(3) At week 8, FML 0.1%
(4) At week 12, LE 0.5% gel
(5) At month 3, MP 1% + CsA
(6) At month 3, LE 0.5% + CsA

## Analysis 2.9. Comparison 2: Steroids versus CsA, Outcome 9: Corneal fluorescein staining scores—Bausch: LE alone

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Singla 2019 (1) | 2.56 | 1.29 | 70 | 3.21 | 1.44 | 70 | 21.4% | -0.47 [-0.81 , -0.14] |
| Byun 2012 (2) | 1.35 | 1.57 | 21 | 1.4 | 1.05 | 20 | 13.2% | -0.04 [-0.65 , 0.58] |
| Wan 2012 (3) | 4.1 | 2.3 | 38 | 4 | 2.1 | 30 | 16.7% | 0.04 [-0.43 , 0.52] |
| Sheppard 2014 (4) | 1.9 | 2.3 | 57 | 1.5 | 2.2 | 55 | 20.2% | 0.18 [-0.19 , 0.55] |
| Bausch 2013 (5) | -0.7 | 3.01 | 36 | -1.6 | 2.46 | 33 | 16.8% | 0.32 [-0.15 , 0.80] |
| Lin 2015 (6) | -2.1 | 0.79 | 19 | -2.51 | 0.85 | 16 | 11.8% | 0.49 [-0.19 , 1.17] |
| **Total (95% CI)** | | | **241** | | | **224** | **100.0%** | **0.05 [-0.25 , 0.35]** |

Heterogeneity: Tau² = 0.08; Chi² = 12.29, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable





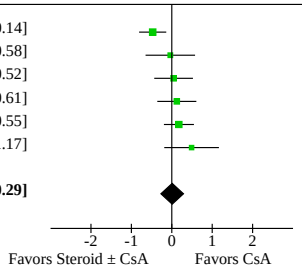
**Footnotes**
(1) At month 3, LE 0.5% + CsA; NEI grading
(2) At month 3, MP 1% + CsA; NEI grading
(3) At week 8, LE 0.5% alone
(4) At day 60 (OD), LE 0.5% + CsA; NEI grading
(5) At week 12, LE gel 0.5% alone; NEI grading
(6) At week 8, FML 0.1% alone

**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.10. Comparison 2: Steroids versus CsA, Outcome 10: Corneal fluorescein staining score—Bausch: LE + CsA

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Singla 2019 (1) | 2.56 | 1.29 | 70 | 3.21 | 1.44 | 70 | 22.2% | -0.47 [-0.81 , -0.14] |
| Byun 2012 (2) | 1.35 | 1.57 | 21 | 1.4 | 1.05 | 20 | 12.7% | -0.04 [-0.65 , 0.58] |
| Wan 2012 (3) | 4.1 | 2.3 | 38 | 4 | 2.1 | 30 | 16.7% | 0.04 [-0.43 , 0.52] |
| Bausch 2013 (4) | -1.3 | 2.3 | 33 | -1.6 | 2.46 | 33 | 16.5% | 0.12 [-0.36 , 0.61] |
| Sheppard 2014 (5) | 1.9 | 2.3 | 57 | 1.5 | 2.2 | 55 | 20.7% | 0.18 [-0.19 , 0.55] |
| Lin 2015 (6) | -2.1 | 0.79 | 19 | -2.51 | 0.85 | 16 | 11.2% | 0.49 [-0.19 , 1.17] |
| **Total (95% CI)** | | | **238** | | | **224** | **100.0%** | **0.01 [-0.27 , 0.29]** |

Heterogeneity: Tau² = 0.06; Chi² = 10.61, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



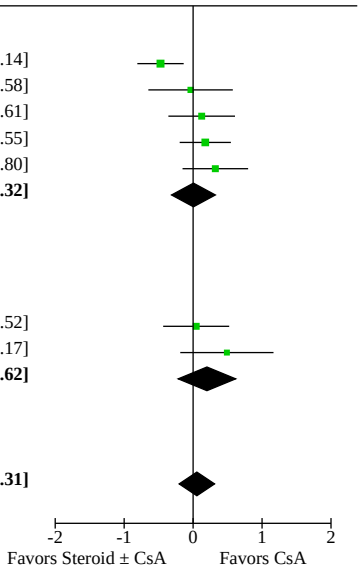


**Footnotes**
(1) At month 3, LE 0.5% + CsA; NEI grading
(2) At month 3, MP 1% + CsA; NEI grading
(3) At week 8, LE 0.5% alone
(4) At week 12, LE gel 0.5% + CsA; NEI grading
(5) At day 60 (OD), LE 0.5% + CsA; NEI grading
(6) At week 8, FML 0.1% alone

**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.11. Comparison 2: Steroids versus CsA, Outcome 11: Corneal fluorescein staining score—by grading system

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.11.1 NEI grading system** | | | | | | | | |
| Singla 2019 (1) | 2.56 | 1.29 | 70 | 3.21 | 1.44 | 70 | 19.1% | -0.47 [-0.81 , -0.14] |
| Byun 2012 (2) | 1.35 | 1.57 | 21 | 1.4 | 1.05 | 20 | 10.8% | -0.04 [-0.65 , 0.58] |
| Bausch 2013 (3) | -1.3 | 2.3 | 33 | -1.6 | 2.46 | 33 | 14.1% | 0.12 [-0.36 , 0.61] |
| Sheppard 2014 (4) | 1.9 | 2.3 | 57 | 1.5 | 2.2 | 55 | 17.8% | 0.18 [-0.19 , 0.55] |
| Bausch 2013 (5) | -0.7 | 3.01 | 36 | -1.6 | 2.46 | 33 | 14.4% | 0.32 [-0.15 , 0.80] |
| **Subtotal (95% CI)** | | | **217** | | | **211** | **76.2%** | **0.01 [-0.31 , 0.32]** |
| Heterogeneity: Tau² = 0.08; Chi² = 10.36, df = 4 (P = 0.03); I² = 61% | | | | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.98) | | | | | | | | |
| **2.11.2 Other grading system** | | | | | | | | |
| Wan 2012 (6) | 4.1 | 2.3 | 38 | 4 | 2.1 | 30 | 14.3% | 0.04 [-0.43 , 0.52] |
| Lin 2015 (7) | -2.1 | 0.79 | 19 | -2.51 | 0.85 | 16 | 9.6% | 0.49 [-0.19 , 1.17] |
| **Subtotal (95% CI)** | | | **57** | | | **46** | **23.8%** | **0.20 [-0.22 , 0.62]** |
| Heterogeneity: Tau² = 0.01; Chi² = 1.11, df = 1 (P = 0.29); I² = 10% | | | | | | | | |
| Test for overall effect: Z = 0.94 (P = 0.34) | | | | | | | | |
| **Total (95% CI)** | | | **274** | | | **257** | **100.0%** | **0.05 [-0.20 , 0.31]** |
| Heterogeneity: Tau² = 0.06; Chi² = 12.55, df = 6 (P = 0.05); I² = 52% | | | | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0% | | | | | | | | |

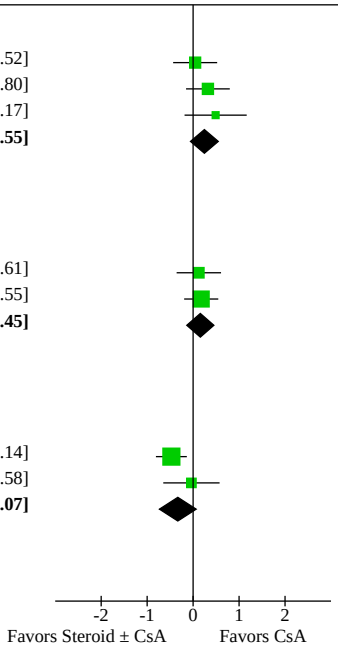



**Footnotes**

(1) At month 3, LE 0.5% + CsA; NEI grading
(2) At month 3, MP 1% + CsA; NEI grading
(3) At week 12, LE 0.5% gel + CsA; NEI grading
(4) At day 60 (OD), LE 0.5% + CsA; NEI grading
(5) At week 12, LE 0.5% gel; NEI grading
(6) At week 8, LE 0.5%
(7) At week 8, FML 0.1%

## Analysis 2.12. Comparison 2: Steroids versus CsA, Outcome 12: Corneal fluorescein staining score—by regimen

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.12.1 Steroid alone vs. CsA 0.05%** | | | | | | | | |
| Wan 2012 (1) | 4.1 | 2.3 | 38 | 4 | 2.1 | 30 | 39.8% | 0.04 [-0.43 , 0.52] |
| Bausch 2013 (2) | -0.7 | 3.01 | 36 | -1.6 | 2.46 | 33 | 40.3% | 0.32 [-0.15 , 0.80] |
| Lin 2015 (3) | -2.1 | 0.79 | 19 | -2.51 | 0.85 | 16 | 19.9% | 0.49 [-0.19 , 1.17] |
| **Subtotal (95% CI)** | | | **93** | | | **79** | **100.0%** | **0.25 [-0.06 , 0.55]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.59 (P = 0.11) | | | | | | | | |
| **2.12.2 Steroid run-in before intitiating CsA 0.05%** | | | | | | | | |
| Bausch 2013 (4) | -1.3 | 2.3 | 33 | -1.6 | 2.46 | 33 | 37.1% | 0.12 [-0.36 , 0.61] |
| Sheppard 2014 (5) | 1.9 | 2.3 | 57 | 1.5 | 2.2 | 55 | 62.9% | 0.18 [-0.19 , 0.55] |
| **Subtotal (95% CI)** | | | **90** | | | **88** | **100.0%** | **0.16 [-0.14 , 0.45]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.30) | | | | | | | | |
| **2.12.3 Steroid run-in concurrently with CsA 0.05%** | | | | | | | | |
| Singla 2019 (6) | 2.56 | 1.29 | 70 | 3.21 | 1.44 | 70 | 67.9% | -0.47 [-0.81 , -0.14] |
| Byun 2012 (7) | 1.35 | 1.57 | 21 | 1.4 | 1.05 | 20 | 32.1% | -0.04 [-0.65 , 0.58] |
| **Subtotal (95% CI)** | | | **91** | | | **90** | **100.0%** | **-0.33 [-0.73 , 0.07]** |
| Heterogeneity: Tau² = 0.03; Chi² = 1.50, df = 1 (P = 0.22); I² = 33% | | | | | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | | | | | |
| Test for subgroup differences: Chi² = 5.52, df = 2 (P = 0.06), I² = 63.8% | | | | | | | | |

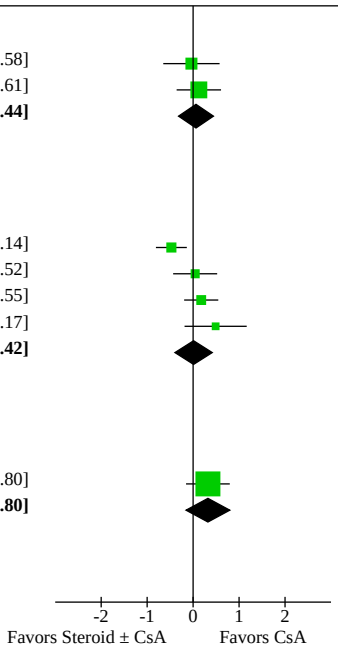



**Footnotes**

(1) At week 8, LE 0.5%
(2) At week 12, LE 0.5% gel
(3) At week 8, FML 0.1%
(4) At week 12, LE 0.5% gel + CsA
(5) At day 60 (OD), LE 0.5% + CsA
(6) At month 3, LE 0.5% + CsA
(7) At month 3, MP 1% + CsA

## Analysis 2.13. Comparison 2: Steroids versus CsA, Outcome 13: Corneal fluorescein staining score—by steroid treatment duration

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.13.1 For 3-4 weeks** | | | | | | | | |
| Byun 2012 (1) | 1.35 | 1.57 | 21 | 1.4 | 1.05 | 20 | 38.3% | -0.04 [-0.65 , 0.58] |
| Bausch 2013 (2) | -1.3 | 2.3 | 33 | -1.6 | 2.46 | 33 | 61.7% | 0.12 [-0.36 , 0.61] |
| **Subtotal (95% CI)** | | | **54** | | | **53** | **100.0%** | **0.06 [-0.32 , 0.44]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | | | | |
| **2.13.2 For 8 weeks** | | | | | | | | |
| Singla 2019 (3) | 2.56 | 1.29 | 70 | 3.21 | 1.44 | 70 | 29.4% | -0.47 [-0.81 , -0.14] |
| Wan 2012 (4) | 4.1 | 2.3 | 38 | 4 | 2.1 | 30 | 24.3% | 0.04 [-0.43 , 0.52] |
| Sheppard 2014 (5) | 1.9 | 2.3 | 57 | 1.5 | 2.2 | 55 | 28.1% | 0.18 [-0.19 , 0.55] |
| Lin 2015 (6) | -2.1 | 0.79 | 19 | -2.51 | 0.85 | 16 | 18.2% | 0.49 [-0.19 , 1.17] |
| **Subtotal (95% CI)** | | | **184** | | | **171** | **100.0%** | **0.01 [-0.39 , 0.42]** |
| Heterogeneity: Tau² = 0.12; Chi² = 10.07, df = 3 (P = 0.02); I² = 70% | | | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | | | |
| **2.13.3 For 12 weeks** | | | | | | | | |
| Bausch 2013 (7) | -0.7 | 3.01 | 36 | -1.6 | 2.46 | 33 | 100.0% | 0.32 [-0.15 , 0.80] |
| **Subtotal (95% CI)** | | | **36** | | | **33** | **100.0%** | **0.32 [-0.15 , 0.80]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.06, df = 2 (P = 0.59), I² = 0% | | | | | | | | |

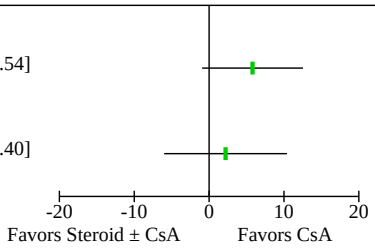



**Footnotes**

(1) At month 3, MP 1% + CsA for 3 weeks before tapering
(2) At week 12, LE 0.5% gel for 2 weeks, adding CsA for concurrent use for another 2 weeks, followed by CsA alone for 8 weeks
(3) At month 3, LE 0.5% 4 times a day for 2 weeks and then twice per day for another 6 weeks; CsA for 3 months
(4) At week 8, LE 0.5%
(5) At day 60 (OD), LE 0.5% 4 times a day for 2 weeks followed by concurrent CsA and LE twice per day for the rest of the study
(6) At week 8, FML 0.1%
(7) At week 12, LE 0.5% gel

## Analysis 2.14. Comparison 2: Steroids versus CsA, Outcome 14: Tear osmolarity

| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.14.1 LE gel 0.5% alone** | | | | | | | |
| Bausch 2013 (1) | 4.3 | 9.88 | 36 | -1.5 | 17.33 | 33 | 5.80 [-0.94 , 12.54] |
| **2.14.2 LE gel 0.5% plus CsA** | | | | | | | |
| Bausch 2013 (1) | 0.7 | 16.67 | 33 | -1.5 | 17.33 | 33 | 2.20 [-6.00 , 10.40] |

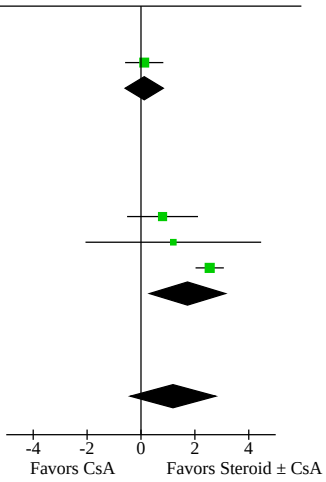



**Footnotes**

(1) At week 12

## Analysis 2.15. Comparison 2: Steroids versus CsA, Outcome 15: Schirmer's test

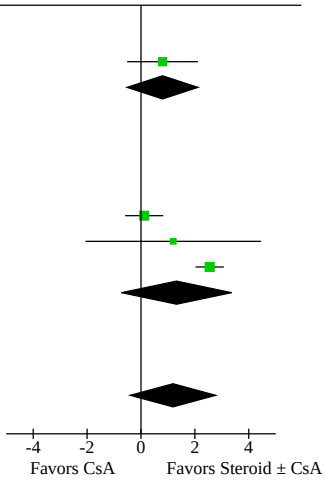
| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.15.1 Steroid alone** | | | | | | | | |
| Wan 2012 (1) | 3.88 | 1.43 | 38 | 3.76 | 1.52 | 30 | 29.8% | 0.12 [-0.59 , 0.83] |
| **Subtotal (95% CI)** | | | **38** | | | **30** | **29.8%** | **0.12 [-0.59 , 0.83]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | | | |
| **2.15.2 Combination** | | | | | | | | |
| Byun 2012 (2) | 10.8 | 2.67 | 21 | 10 | 1.49 | 20 | 26.0% | 0.80 [-0.52 , 2.12] |
| Sheppard 2014 (3) | 12.3 | 8.9 | 57 | 11.1 | 8.7 | 55 | 13.5% | 1.20 [-2.06 , 4.46] |
| Singla 2019 (4) | 10.64 | 1.81 | 70 | 8.09 | 1.32 | 70 | 30.6% | 2.55 [2.03 , 3.07] |
| **Subtotal (95% CI)** | | | **148** | | | **145** | **70.2%** | **1.73 [0.32 , 3.13]** |
| Heterogeneity: Tau² = 0.97; Chi² = 6.30, df = 2 (P = 0.04); I² = 68% | | | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.02) | | | | | | | | |
| **Total (95% CI)** | | | **186** | | | **175** | **100.0%** | **1.19 [-0.40 , 2.77]** |
| Heterogeneity: Tau² = 2.06; Chi² = 30.81, df = 3 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 1.47 (P = 0.14) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.99, df = 1 (P = 0.05), I² = 74.9% | | | | | | | | |




**Footnotes**
(1) At week 8, LE 0.5%
(2) At month 3, MP 1% + CsA
(3) At day 60, LE 0.5% + CsA
(4) At month 3, LE 0.5% + CsA

## Analysis 2.16. Comparison 2: Steroids versus CsA, Outcome 16: Schirmer's test—by steroid type

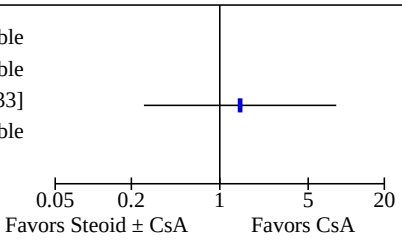
| Study or Subgroup | Steroid ± CsA Mean | SD | Total | Cyclosporine A (CsA) Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.16.1 Ketone steroid: MP + CsA** | | | | | | | | |
| Byun 2012 (1) | 10.8 | 2.67 | 21 | 10 | 1.49 | 20 | 26.0% | 0.80 [-0.52 , 2.12] |
| **Subtotal (95% CI)** | | | **21** | | | **20** | **26.0%** | **0.80 [-0.52 , 2.12]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.19 (P = 0.23) | | | | | | | | |
| **2.16.2 Ester steroid: LE ± CsA** | | | | | | | | |
| Wan 2012 (2) | 3.88 | 1.43 | 38 | 3.76 | 1.52 | 30 | 29.8% | 0.12 [-0.59 , 0.83] |
| Sheppard 2014 (3) | 12.3 | 8.9 | 57 | 11.1 | 8.7 | 55 | 13.5% | 1.20 [-2.06 , 4.46] |
| Singla 2019 (4) | 10.64 | 1.81 | 70 | 8.09 | 1.32 | 70 | 30.6% | 2.55 [2.03 , 3.07] |
| **Subtotal (95% CI)** | | | **165** | | | **155** | **74.0%** | **1.32 [-0.72 , 3.36]** |
| Heterogeneity: Tau² = 2.61; Chi² = 29.24, df = 2 (P < 0.00001); I² = 93% | | | | | | | | |
| Test for overall effect: Z = 1.27 (P = 0.21) | | | | | | | | |
| **Total (95% CI)** | | | **186** | | | **175** | **100.0%** | **1.19 [-0.40 , 2.77]** |
| Heterogeneity: Tau² = 2.06; Chi² = 30.81, df = 3 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 1.47 (P = 0.14) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.68), I² = 0% | | | | | | | | |




**Footnotes**
(1) At month 3, MP 1% + CsA
(2) At week 8, LE 0.5%
(3) At day 60, LE 0.5% run-in for 2 weeks before adding CsA for 6 weeks
(4) At month 3, LE 0.5% + CsA

### Analysis 2.17. Comparison 2: Steroids versus CsA, Outcome 17: Proportion of participants with increased IOP

| Study or Subgroup | Steroids ± CsA Events | Steroids ± CsA Total | Cyclosporine A (CsA) Events | Cyclosporine A (CsA) Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Byun 2012 (1) | 0 | 21 | 0 | 23 | Not estimable |
| Lin 2015 (2) | 0 | 19 | 0 | 16 | Not estimable |
| Sheppard 2014 (3) | 3 | 57 | 2 | 55 | 1.45 [0.25 , 8.33] |
| Singla 2019 (4) | 0 | 70 | 0 | 70 | Not estimable |

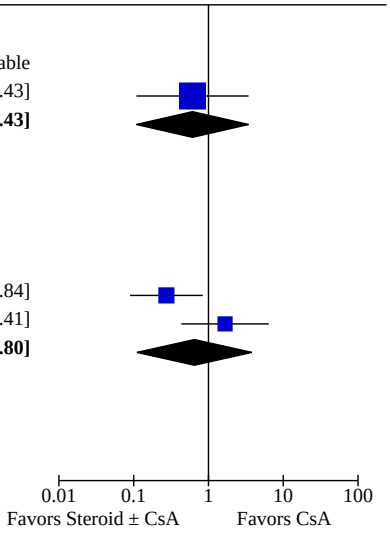



**Footnotes**

(1) MP 1% + CsA for 3 months
(2) FML 0.1% for 8 weeks
(3) LE 0.5% run-in for 2 weeks before adding CsA 0.05% on Day 15 to Day 60
(4) LE 0.5% + CsA for 3 months, study period was 6 months

### Analysis 2.18. Comparison 2: Steroids versus CsA, Outcome 18: Proportion of participants with any ocular complication

| Study or Subgroup | Steroid ± CsA Events | Steroid ± CsA Total | Cyclosporine A (CsA) Events | Cyclosporine A (CsA) Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.18.1 Steroid alone** | | | | | | |
| Wan 2012 (1) | 0 | 19 | 0 | 15 | | Not estimable |
| Bausch 2013 (2) | 2 | 36 | 3 | 33 | 100.0% | 0.61 [0.11 , 3.43] |
| **Subtotal (95% CI)** | | **55** | | **48** | **100.0%** | **0.61 [0.11 , 3.43]** |
| Total events: | 2 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.56 (P = 0.58) | | | | | | |
| **2.18.2 Steroid plus CsA** | | | | | | |
| Byun 2012 (3) | 3 | 21 | 12 | 23 | 52.3% | 0.27 [0.09 , 0.84] |
| Bausch 2013 (4) | 5 | 33 | 3 | 33 | 47.7% | 1.67 [0.43 , 6.41] |
| **Subtotal (95% CI)** | | **54** | | **56** | **100.0%** | **0.65 [0.11 , 3.80]** |
| Total events: | 8 | | 15 | | | |
| Heterogeneity: Tau² = 1.23; Chi² = 4.09, df = 1 (P = 0.04); I² = 76% | | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | |




**Footnotes**

(1) Treatment duration 8 weeks, LE 0.5% alone
(2) Treatment duration 12 weeks, LE 0.5% gel alone
(3) Treatment duration 12 weeks, MP 1% + CsA
(4) Treatment duration 12 weeks, LE 0.5% gel + CsA

## APPENDICES

### Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Dry Eye Syndromes] explode all trees
#2 (dry near/2 eye*)
#3 (ocular near/2 dry*)
#4 MeSH descriptor: [Tears] explode all trees
#5 tear*
#6 MeSH descriptor: [Xerophthalmia] explode all trees

#7 xerophthalmi*
#8 MeSH descriptor: [Vitamin A Deficiency] explode all trees
#9 ("vitamin A" near/3 deficien*)
#10 ("avitaminosis a" or (retinol near/1 deficien*) or "hypovitaminosis A")
#11 MeSH descriptor: [Keratoconjunctivitis Sicca] explode all trees
#12 (Keratoconjunctiv* or "kerato conjunctivitis")
#13 MeSH descriptor: [Sjogren's Syndrome] explode all trees
#14 ((Sjogren* or Sjoegren*) near/2 (syndrom* or disease*))
#15 (sicca next/1 syndrom*)
#16 MeSH descriptor: [Stevens-Johnson Syndrome] explode all trees
#17 (Steven* and Johnson and (syndrom* or disease*))
#18 MeSH descriptor: [Pemphigoid, Benign Mucous Membrane] explode all trees
#19 (Benign and Muco* and Pemphigoid*)
#20 (Cicatricial near/2 Pemphigoid*)
#21 blepharoconjunctiviti*
#22 MeSH descriptor: [Meibomian Glands] explode all trees
#23 (meibomian or tarsal)
#24 MeSH descriptor: [Lacrimal Apparatus Diseases] explode all trees
#25 (lacrima* or epiphora)
#26 {OR #1-#25}
#27 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#28 corticosteroid* OR glucocorticoid* OR mineralocorticoid* OR "adrenal cortex hormone" OR "adrenal cortex hormones" OR "adrenal cortical hormone" OR "adrenal cortical hormones" OR "adrenocortical hormone" OR "adrenocortical hormones" OR adrenocorticosteroid* OR corticoid* OR steroid*
#29 MeSH descriptor: [Betamethasone] explode all trees
#30 Betamethasone* OR adbeon OR becasone OR beprogel OR "beta methason" OR "beta methasone" OR "beta-phos/ac" OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethason OR betamethasonum OR betamethazone OR betason OR betnasol OR betnelan OR "betnesol v" OR "betnovate a" OR betsolan OR betsolon OR betsopart OR celestan OR celestene OR celeston OR celestona OR celestone OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR methasone OR "nsc 39470" OR nsc39470 OR ophtamesone OR "rg 833" OR rg833 OR rinderon OR "sch 4831" OR sch4831 OR walacort OR "378-44-9"
#31 "clobetasone butyrate" OR "cci 5537" OR cci5537 OR "clobetasone 17 butyrate" OR emovate OR eumovate OR "gr 2 1214" OR "gr 2-1214" OR "gr 21214" OR "gr2-1214" OR kindavate OR "sn 203" OR sn203 OR trimovate OR "25122-57-0"
#32 MeSH descriptor: [Dexamethasone] explode all trees
#33 Dexamethasone* OR adrecort OR adrenocot OR "aeroseb dex" OR "aeroseb-d" OR aflucoson OR aflucosone OR alfalyl OR anaflogistico OR aphtasolon OR arcodexan OR arcodexane OR artrosone OR auxiron OR azium OR bidexol OR "bisu ds" OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR corsone OR cortastat OR cortidex OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR "dacortina fuerte" OR "dacortine fuerte" OR dalalone OR danasone OR "de-sone la" OR decacortin OR decadeltosona OR decadeltosone OR decaderm OR decadion OR decadran OR decadron OR decadronal OR decadrone OR decaesadril OR decagel OR decaject OR decalix OR decameth OR decamethasone OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekacort OR delladec OR deltafluoren OR deltafluorene OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton OR desametone OR desigdron OR "dexa cortisyl" OR "dexa dabrosan" OR "dexa korti" OR "dexa scherosan" OR "dexa scherozon" OR "dexa scherozone" OR "dexa-p" OR "dexacen 4" OR dexachel OR dexacort OR dexacortal OR dexacorten OR dexacortin OR dexacortisyl OR dexadabroson OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson OR dexamesone OR dexametason OR dexametasone OR dexameth OR dexamethason OR dexamethazon OR dexamethazone OR dexamethonium OR dexamonozon OR dexan OR dexane OR dexano OR dexapot OR dexascheroson OR dexascherozon OR dexascherozone OR dexason OR dexasone OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR dexpak OR dextelan OR dextenza OR dextrasone OR dexycu OR dezone OR dibasona OR doxamethasone OR esacortene OR "ex s1" OR exadion OR exadione OR firmalone OR "fluormethyl prednisolone" OR fluormethylprednisolon OR fluormethylprednisolone OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortecortin OR gammacorten OR gammacortene OR grosodexon OR grosodexone OR hemady OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR "isopto dex" OR "isopto maxidex" OR "isopto-dex" OR "isopto-maxidex" OR isoptodex OR isoptomaxidex OR "lokalison f" OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson OR mephamesone OR metasolon OR metasolone OR "methazon ion" OR "methazone ion" OR methazonion OR methazonione OR methylfluorprednisolone OR "metisone lafi" OR mexasone OR millicorten OR millicortenol OR "mk 125" OR mk125 OR mymethasone OR neoforderx OR neofordex OR nisomethasona OR novocort OR "nsc 34521" OR nsc34521 OR "oftan-dexa" OR opticorten OR opticortinol OR oradexan OR oradexon OR oradexone OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR "predni f tablinen" OR "predni-f" OR "prednisolone f" OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR triamcimetil OR vexamet OR visumetazone OR visumethazone OR "50-02-2"
#34 difluprednate* OR "cm 9155" OR cm9155 OR durezol OR epitopic OR myser OR "w 6309" OR w6309 OR "warner 6309" OR ENV905 OR "23674-86-4"
#35 MeSH descriptor: [Fluorometholone] explode all trees

#36 Fluorometholone* OR cortilet OR cortisdin OR delmeson OR delmesone OR efflumidex OR eflone OR flosef OR fluaton OR flucon OR fluforte liquifilm OR flulon OR flumelon OR flumetholon OR flumetholone OR flumex OR flumexo OR fluometholone OR fluoph OR "fluoro ophtal" OR "fluor-op" OR fluorlon OR fluormetholon OR fluoromethalone OR fluoropos OR fml OR fuluson OR isopto flucon OR loticort OR methasite OR oxylone OR "426-13-1"
#37 MeSH descriptor: [Loteprednol Etabonate] explode all trees
#38 Loteprednol* OR alrex OR "cddd 5604" OR cddd5604 OR CEHOAC OR "Chloromethyl 17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate" OR "17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate, Chloromethyl" OR "Chloromethyl 17 ethoxycarbonyloxy 11 hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate" OR eysuvis OR "hgp 1" OR hgp1 OR inveltys OR "kpi 121" OR kpi121 OR "le-mpp" OR lotemax OR loterex OR loterox OR lotesoft OR "p 5604" OR p5604 OR "82034-46-6"
#39 MeSH descriptor: [Prednisolone] explode all trees
#40 Prednisolone* OR adelcort OR antisolon OR antisolone OR aprednislon OR aprednislone OR benisolon OR benisolone OR berisolon OR berisolone OR caberdelta OR capsoid OR "co hydeltra" OR codelcortone OR compresolon OR cortadeltona OR cortadeltone OR cortalone OR cortelinter OR cortisolone OR cotolone OR dacortin OR dacrotin OR decaprednil OR "decortin h" OR decortril OR "dehydro cortex" OR "dehydro hydrocortisone" OR "dehydro hydrocortisone" OR dehydrocortex OR dehydrocortisol OR dehydrocortisole OR dehydrohydrocortison OR dehydrohydrocortisone OR delcortol OR "delta 1 17 hydroxycorticosterone 21 acetate" OR "delta 1 hydrocortisone" OR "delta cortef" OR "delta cortril" OR "delta ef cortelan" OR "delta f" OR "delta hycortol" OR "delta hydrocortisone" OR "delta hydrocortisone" OR "delta ophticor" OR "delta stab" OR "delta-cortef" OR "delta1 dehydrocortisol" OR "delta1 dehydrohydrocortisone" OR "delta1 hydrocortisone" OR deltacortef OR deltacortenolo OR deltacortil OR deltacortoil OR deltacortril OR deltaderm OR deltaglycortril OR deltahycortol OR deltahydrocortison OR deltahydrocortisone OR deltaophticor OR deltasolone OR deltastab OR deltidrosol OR deltisilone OR deltisolon OR deltisolone OR deltolasson OR deltolassone OR deltosona OR deltosone OR "depo-predate" OR dermosolon OR dhasolone OR DiAdresonF OR "di adreson f" OR "di adresone f" OR "di-adreson-f" OR "diadreson f" OR "diadresone f" OR dicortol OR domucortone OR encortelon OR encortelone OR encortolon OR equisolon OR "fernisolone-p" OR glistelone OR hefasolon OR "hostacortin h" OR hydeltra OR hydeltrone OR hydrelta OR hydrocortancyl OR hydrocortidelt OR hydrodeltalone OR hydrodeltisone OR hydroretrocortin OR hydroretrocortine OR inflanefran OR insolone OR "keteocort h" OR "key-pred" OR lenisolone OR leocortol OR liquipred OR "lygal kopftinktur n" OR mediasolone OR meprisolon OR meprisolone OR metacortalon OR metacortalone OR metacortandralon OR metacortandralone OR metacortelone OR "meti derm" OR meticortelone OR metiderm OR morlone OR mydrapred OR "neo delta" OR nisolon OR nisolone OR "nsc 9120" OR nsc9120 OR opredsone OR panafcortelone OR panafcortolone OR panafort OR paracortol OR phlogex OR "pre cortisyl" OR preconin OR precortalon OR precortancyl OR precortisyl OR "pred-ject-50" OR "predacort 50" OR "predaject-50" OR "predalone 50" OR predartrina OR predartrine OR predate OR "predate-50" OR predeltilone OR predisole OR predisyr OR "predne dome" OR prednecort OR prednedome OR prednelan OR "predni coelin" OR "predni h tablinen" OR "predni-helvacort" OR prednicoelin OR prednicort OR prednicortelone OR "prednifor drops" OR predniment OR predniretard OR prednis OR prednisil OR prednisolon OR prednisolona OR prednivet OR prednorsolon OR prednorsolone OR predonine OR predorgasolona OR predorgasolone OR "pregna 1, 4 diene 11beta, 17alpha, 21 triol 3, 20 dione" OR prelon OR prelone OR prenilone OR prenin OR prenolone OR preventan OR prezolon OR rubycort OR scherisolon OR scherisolona OR serilone OR solondo OR solone OR solupren OR soluprene OR spiricort OR spolotane OR sterane OR sterolone OR supercortisol OR supercortizol OR taracortelone OR walesolone OR wysolone OR "50-24-8"
#41 {OR #27-#40}
#42 #26 AND #41 in Trials

## Appendix 2. MEDLINE (Ovid) search strategy

1 Randomized Controlled Trial.pt.
2 Controlled Clinical Trial.pt.
3 (randomized or randomised).ab,ti.
4 placebo.ab,ti.
5 drug therapy.fs.
6 randomly.ab,ti.
7 trial.ab,ti.
8 groups.ab,ti.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp dry eye syndromes/
13 (dry adj2 eye*).tw.
14 (ocular adj2 dry*).tw.
15 exp tears/
16 tear*.tw.
17 exp xerophthalmia/
18 xerophthalmi*.tw.
19 exp vitamin A deficiency/
20 (vitamin A adj3 deficien*).tw.
21 (avitaminosis a or retinol deficien* or hypovitaminosis A).tw.
22 exp keratoconjunctivitis sicca/

23 (Keratoconjunctiv* or kerato conjunctivitis).tw.
24 exp Keratoconjunctivitis/
25 limit 24 to yr="1966 - 1985"
26 exp Sjogren's syndrome/
27 ((Sjogren* or Sjoegren*) adj2 (syndrom* or disease*)).tw.
28 sicca syndrom*.tw.
29 exp Stevens Johnson syndrome/
30 (Steven* and Johnson and (syndrom* or disease*)).tw.
31 exp Pemphigoid, Benign Mucous Membrane/
32 Benign Muco* Pemphigoid*.tw.
33 (Cicatricial adj2 Pemphigoid*).tw.
34 blepharoconjunctiviti$.tw.
35 exp meibomian glands/
36 (meibomian or tarsal).tw.
37 exp lacrimal apparatus diseases/
38 (lacrima* or epiphora).tw.
39 or/12-23,25-38
40 exp Adrenal Cortex Hormones/
41 (corticosteroid* or glucocorticoid* or mineralocorticoid* or "adrenal cortex hormone" or "adrenal cortex hormones" or "adrenal cortical hormone" or "adrenal cortical hormones" or "adrenocortical hormone" or "adrenocortical hormones" or adrenocorticosteroid* or corticoid* or steroid*).tw.
42 exp Betamethasone/
43 (Betamethasone* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or "beta-phos/ac" or betacortril or betadexamethasone or betametasone or betamethasolone or betamethason or betamethasonum or betamethazone or betason or betnasol or betnelan or "betnesol v" or "betnovate a" or betsolan or betsolon or betsopart or celestan or celestene or celeston or celestona or celestone or cellestoderm or cidoten or dermobet or diprolen or flubenisolone or methasone or "nsc 39470" or nsc39470 or ophtamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walacort or "378-44-9").tw,rn.
44 ("clobetasone butyrate" or "cci 5537" or cci5537 or "clobetasone 17 butyrate" or emovate or eumovate or "gr 2 1214" or "gr 2-1214" or "gr 21214" or "gr2-1214" or kindavate or "sn 203" or sn203 or trimovate or "25122-57-0").tw,rn.
45 exp Dexamethasone/
46 (Dexamethasone* or adrecort or adrenocot or "aeroseb dex" or "aeroseb-d" or aflucoson or aflucosone or alfalyl or anaflogistico or aphtasolon or arcodexan or arcodexane or artrosone or auxiron or azium or bidexol or "bisu ds" or calonat or cebedex or cetadexon or colofoam or corsona or corsone or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or "dacortina fuerte" or "dacortine fuerte" or dalalone or danasone or "de-sone la" or decacortin or decadeltosona or decadeltosone or decaderm or decadion or decadran or decadron or decadronal or decadrone or decaesadril or decagel or decaject or decalix or decameth or decamethasone or decasone or decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or desacort or desacortone or desadrene or desalark or desameton or desametone or desigdron or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexa-p" or "dexacen 4" or dexachel or dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabroson or dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or dexametason or dexametasone or dexameth or dexamethason or dexamethazon or dexamethazone or dexamethonium or dexamonozon or dexan or dexane or dexano or dexapot or dexascheroson or dexascherozon or dexascherozone or dexason or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or dexpak or dextelan or dextenza or dextrasone or dexycu or dezone or dibasona or doxamethasone or esacortene or "ex s1" or exadion or exadione or firmalone or "fluormethyl prednisolone" or fluormethylprednisolon or fluormethylprednisolone or fluormone or fluorocort or fluorodelta or fluoromethylprednisolone or fortecortin or gammacorten or gammacortene or grosodexon or grosodexone or hemady or hexadecadiol or hexadecadrol or hexadiol or hexadrol or isnacort or "isopto dex" or "isopto maxidex" or "isopto-dex" or "isopto-maxidex" or isoptodex or isoptomaxidex or "lokalison f" or loverine or luxazone or marvidione or maxidex or mediamethasone or megacortin or mephameson or mephamesone or metasolon or metasolone or "methazon ion" or "methazone ion" or methazonion or methazonione or methylfluorprednisolone or "metisone lafi" or mexasone or millicorten or millicortenol or "mk 125" or mk125 or mymethasone or neoforderx or neofordex or nisomethasona or novocort or "nsc 34521" or nsc34521 or "oftan-dexa" or opticorten or opticortinol or oradexan or oradexon or oradexone or orgadrone or ozurdex or pidexon or policort or posurdex or "predni f tablinen" or "predni-f" or "prednisolone f" or prodexona or prodexone or sanamethasone or santenson or santeson or sawasone or solurex or spoloven or sterasone or thilodexine or triamcimetil or vexamet or visumetazone or visumethazone or "50-02-2").tw,rn.
47 (difluprednate* or "cm 9155" or cm9155 or durezol or epitopic or myser or "w 6309" or w6309 or "warner 6309" or ENV905 or "23674-86-4").tw,rn.
48 exp Fluorometholone/
49 (Fluorometholone* or cortilet or cortisdin or delmeson or delmesone or efflumidex or eflone or flosef or fluaton or flucon or fluforte liquifilm or flulon or flumelon or flumetholon or flumetholone or flumex or flumexo or fluometholone or fluoph or "fluoro ophtal" or "fluor-op" or fluorlon or fluormetholon or fluoromethalone or fluoropos or fml or fuluson or isopto flucon or loticort or methasite or oxylone or "426-13-1").tw,rn.
50 exp Loteprednol Etabonate/

51 (Loteprednol* or alrex or "cddd 5604" or cddd5604 or CEHOAC or "Chloromethyl 17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate" or "17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate, Chloromethyl" or "Chloromethyl 17 ethoxycarbonyloxy 11 hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate" or eysuvis or "hgp 1" or hgp1 or inveltys or "kpi 121" or kpi121 or "le-mpp" or lotemax or loterex or loterox or lotesoft or "p 5604" or p5604 or "82034-46-6").tw,rn.
52 exp Prednisolone/
53 (Prednisolone* or adelcort or antisolon or antisolone or aprednislon or aprednislone or benisolon or benisolone or berisolon or berisolone or caberdelta or capsoid or "co hydeltra" or codelcortone or compresolon or cortadeltona or cortadeltone or cortalone or cortelinter or cortisolone or cotolone or dacortin or dacrotin or decaprednil or "decortin h" or decortril or "dehydro cortex" or "dehydro hydrocortisone" or "dehydro hydrocortisone" or dehydrocortex or dehydrocortisol or dehydrocortisole or dehydrohydrocortison or dehydrohydrocortisone or delcortol or "delta 1 17 hydroxycorticosterone 21 acetate" or "delta 1 hydrocortisone" or "delta cortef" or "delta cortril" or "delta ef cortelan" or "delta f" or "delta hycortol" or "delta hydrocortisone" or "delta hydrocortisone" or "delta ophticor" or "delta stab" or "delta-cortef" or "delta1 dehydrocortisol" or "delta1 dehydrohydrocortisone" or "delta1 hydrocortisone" or deltacortef or deltacortenolo or deltacortil or deltacortoil or deltacortril or deltaderm or deltaglycortril or deltahycortol or deltahydrocortison or deltahydrocortisone or deltaophticor or deltasolone or deltastab or deltidrosol or deltisilone or deltisolon or deltisolone or deltolasson or deltolassone or deltosona or deltosone or "depo-predate" or dermosolon or dhasolone or DiAdresonF or "di adreson f" or "di adresone f" or "di-adreson-f" or "diadreson f" or "diadresone f" or dicortol or domucortone or encortelon or encortelone or encortolon or equisolon or "fernisolone-p" or glistelone or hefasolon or "hostacortin h" or hydeltra or hydeltrone or hydrelta or hydrocortancyl or hydrocortidelt or hydrodeltalone or hydrodeltisone or hydroretrocortin or hydroretrocortine or inflanefran or insolone or "keteocort h" or "key-pred" or lenisolone or leocortol or liquipred or "lygal kopftinktur n" or mediasolone or meprisolon or meprisolone or metacortalon or metacortalone or metacortandralon or metacortandralone or metacortelone or "meti derm" or meticortelone or metiderm or morlone or mydrapred or "neo delta" or nisolon or nisolone or "nsc 9120" or nsc9120 or opredsone or panafcortelone or panafcortolone or panafort or paracortol or phlogex or "pre cortisyl" or preconin or precortalon or precortancyl or precortisyl or "pred-ject-50" or "predacort 50" or "predaject-50" or "predalone 50" or predartrina or predartrine or predate or "predate-50" or predeltilone or predisole or predisyr or "predne dome" or prednecort or prednedome or prednelan or "predni coelin" or "predni h tablinen" or "predni-helvacort" or prednicoelin or prednicort or prednicortelone or "prednifor drops" or predniment or predniretard or prednis or prednisil or prednisolon or prednisolona or prednivet or prednorsolon or prednorsolone or predonine or predorgasolona or predorgasolone or "pregna 1, 4 diene 11beta, 17alpha, 21 triol 3, 20 dione" or prelon or prelone or prenilone or prenin or prenolone or preventan or prezolon or rubycort or scherisolon or scherisolona or serilone or solondo or solone or solupren or soluprene or spiricort or spolotane or sterane or sterolone or supercortisol or supercortizol or taracortelone or walesolone or wysolone or "50-24-8").tw,rn.
54 or/40-53
55 39 and 54
56 11 and 55

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

## Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp

#26 'evaluation'/exp
#27 'prospective study'/` exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'dry eye'/exp
#34 (dry NEAR/2 eye*):ab,ti,kw
#35 (ocular NEAR/2 dry*):ab,ti,kw
#36 'lacrimal fluid'/exp
#37 tear*:ab,ti,kw
#38 'xerophthalmia'/exp
#39 xerophthalmi*:ab,ti,kw
#40 'retinol deficiency'/exp
#41 ('vitamin a' NEAR/3 deficien*):ab,ti,kw
#42 'avitaminosis a':ab,ti,kw OR (retinol NEAR/1 deficien*):ab,ti,kw OR 'hypovitaminosis a':ab,ti,kw
#43 'keratoconjunctivitis sicca'/exp
#44 keratoconjunctiv*:ab,ti,kw OR 'kerato conjunctivitis':ab,ti,kw
#45 'sjoegren syndrome'/exp
#46 ((sjogren* OR sjoegren*) NEAR/2 (syndrom* OR disease*)):ab,ti,kw
#47 (sicca NEXT/1 syndrom*):ab,ti,kw
#48 'stevens johnson syndrome'/exp
#49 steven*:ab,ti,kw AND johnson:ab,ti,kw AND (syndrom*:ab,ti,kw OR disease*:ab,ti,kw)
#50 'mucous membrane pemphigoid'/exp
#51 benign AND muco* AND pemphigoid*:ab,ti,kw
#52 (cicatricial NEAR/2 pemphigoid*):ab,ti,kw
#53 blepharoconjunctiviti*:ab,ti,kw
#54 'meibomian gland'/exp
#55 meibomian:ab,ti,kw OR tarsal:ab,ti,kw
#56 'lacrimal gland disease'/exp
#57 lacrima*:ab,ti,kw OR epiphora:ab,ti,kw
#58 #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 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
#59 'corticosteroid'/exp
#60 corticosteroid*:ab,ti,kw,tn OR glucocorticoid*:ab,ti,kw,tn OR mineralocorticoid*:ab,ti,kw,tn OR 'adrenal cortex hormone':ab,ti,kw,tn OR 'adrenal cortex hormones':ab,ti,kw,tn OR 'adrenal cortical hormone':ab,ti,kw,tn OR 'adrenal cortical hormones':ab,ti,kw,tn OR 'adrenocortical hormone':ab,ti,kw,tn OR 'adrenocortical hormones':ab,ti,kw,tn OR adrenocorticosteroid*:ab,ti,kw,tn OR corticoid*:ab,ti,kw,tn OR steroid*:ab,ti,kw,tn
#61 'betamethasone'/exp
#62 betamethasone*:ab,ti,kw,tn,rn OR adbeon:ab,ti,kw,tn,rn OR becasone:ab,ti,kw,tn,rn OR beprogel:ab,ti,kw,tn,rn OR 'beta methason':ab,ti,kw,tn,rn OR 'beta methasone':ab,ti,kw,tn,rn OR 'beta-phos/ac':ab,ti,kw,tn,rn OR betacortril:ab,ti,kw,tn,rn OR betadexamethasone:ab,ti,kw,tn,rn OR betametasone:ab,ti,kw,tn,rn OR betamethasolone:ab,ti,kw,tn,rn OR betamethason:ab,ti,kw,tn,rn OR betamethasonum:ab,ti,kw,tn,rn OR betamethazone:ab,ti,kw,tn,rn OR betason:ab,ti,kw,tn,rn OR betnasol:ab,ti,kw,tn,rn OR betnelan:ab,ti,kw,tn,rn OR 'betnesol v':ab,ti,kw,tn,rn OR 'betnovate a':ab,ti,kw,tn,rn OR betsolan:ab,ti,kw,tn,rn OR betsolon:ab,ti,kw,tn,rn OR betsopart:ab,ti,kw,tn,rn OR celestan:ab,ti,kw,tn,rn OR celestene:ab,ti,kw,tn,rn OR celeston:ab,ti,kw,tn,rn OR celestona:ab,ti,kw,tn,rn OR celestone:ab,ti,kw,tn,rn OR cellestoderm:ab,ti,kw,tn,rn OR cidoten:ab,ti,kw,tn,rn OR dermobet:ab,ti,kw,tn,rn OR diprolen:ab,ti,kw,tn,rn OR flubenisolone:ab,ti,kw,tn,rn OR methasone:ab,ti,kw,tn,rn OR 'nsc 39470':ab,ti,kw,tn,rn OR nsc39470:ab,ti,kw,tn,rn OR ophtamesone:ab,ti,kw,tn,rn OR 'rg 833':ab,ti,kw,tn,rn OR rg833:ab,ti,kw,tn,rn OR rinderon:ab,ti,kw,tn,rn OR 'sch 4831':ab,ti,kw,tn,rn OR sch4831:ab,ti,kw,tn,rn OR walacort:ab,ti,kw,tn,rn OR '378-44-9':ab,ti,kw,tn,rn
#63 'clobetasone butyrate'/exp
#64 'clobetasone butyrate':ab,ti,kw,tn,rn OR 'cci 5537':ab,ti,kw,tn,rn OR cci5537:ab,ti,kw,tn,rn OR 'clobetasone 17 butyrate':ab,ti,kw,tn,rn OR emovate:ab,ti,kw,tn,rn OR eumovate:ab,ti,kw,tn,rn OR 'gr 2 1214':ab,ti,kw,tn,rn OR 'gr 2-1214':ab,ti,kw,tn,rn OR 'gr 21214':ab,ti,kw,tn,rn OR 'gr2-1214':ab,ti,kw,tn,rn OR kindavate:ab,ti,kw,tn,rn OR 'sn 203':ab,ti,kw,tn,rn OR sn203:ab,ti,kw,tn,rn OR trimovate:ab,ti,kw,tn,rn OR '25122-57-0':ab,ti,kw,tn,rn
#65 'dexamethasone'/exp
#66 dexamethasone*:ab,ti,kw,tn,rn OR adrecort:ab,ti,kw,tn,rn OR adrenocot:ab,ti,kw,tn,rn OR 'aeroseb dex':ab,ti,kw,tn,rn OR 'aeroseb-d':ab,ti,kw,tn,rn OR aflucoson:ab,ti,kw,tn,rn OR aflucosone:ab,ti,kw,tn,rn OR alfalyl:ab,ti,kw,tn,rn OR anaflogistico:ab,ti,kw,tn,rn OR aphtasolon:ab,ti,kw,tn,rn OR arcodexan:ab,ti,kw,tn,rn OR arcodexane:ab,ti,kw,tn,rn OR artrosone:ab,ti,kw,tn,rn OR auxiron:ab,ti,kw,tn,rn OR azium:ab,ti,kw,tn,rn OR bidexol:ab,ti,kw,tn,rn OR 'bisu ds':ab,ti,kw,tn,rn OR calonat:ab,ti,kw,tn,rn OR cebedex:ab,ti,kw,tn,rn OR cetadexon:ab,ti,kw,tn,rn OR colofoam:ab,ti,kw,tn,rn OR corsona:ab,ti,kw,tn,rn OR corsone:ab,ti,kw,tn,rn OR cortastat:ab,ti,kw,tn,rn OR cortidex:ab,ti,kw,tn,rn OR cortidexason:ab,ti,kw,tn,rn OR cortidrona:ab,ti,kw,tn,rn OR

cortidrone:ab,ti,kw,tn,rn OR cortisumman:ab,ti,kw,tn,rn OR 'dacortina fuerte':ab,ti,kw,tn,rn OR 'dacortine fuerte':ab,ti,kw,tn,rn OR dalalone:ab,ti,kw,tn,rn OR danasone:ab,ti,kw,tn,rn OR 'de-sone la':ab,ti,kw,tn,rn OR decacortin:ab,ti,kw,tn,rn OR decadeltosona:ab,ti,kw,tn,rn OR decadeltosone:ab,ti,kw,tn,rn OR decaderm:ab,ti,kw,tn,rn OR decadion:ab,ti,kw,tn,rn OR decadran:ab,ti,kw,tn,rn OR decadron:ab,ti,kw,tn,rn OR decadronal:ab,ti,kw,tn,rn OR decadrone:ab,ti,kw,tn,rn OR decaesadril:ab,ti,kw,tn,rn OR decagel:ab,ti,kw,tn,rn OR decaject:ab,ti,kw,tn,rn OR decalix:ab,ti,kw,tn,rn OR decameth:ab,ti,kw,tn,rn OR decamethasone:ab,ti,kw,tn,rn OR decasone:ab,ti,kw,tn,rn OR decaspray:ab,ti,kw,tn,rn OR decasterolone:ab,ti,kw,tn,rn OR decdan:ab,ti,kw,tn,rn OR decilone:ab,ti,kw,tn,rn OR decofluor:ab,ti,kw,tn,rn OR dectancyl:ab,ti,kw,tn,rn OR dekacort:ab,ti,kw,tn,rn OR delladec:ab,ti,kw,tn,rn OR deltafluoren:ab,ti,kw,tn,rn OR deltafluorene:ab,ti,kw,tn,rn OR dergramin:ab,ti,kw,tn,rn OR deronil:ab,ti,kw,tn,rn OR desacort:ab,ti,kw,tn,rn OR desacortone:ab,ti,kw,tn,rn OR desadrene:ab,ti,kw,tn,rn OR desalark:ab,ti,kw,tn,rn OR desameton:ab,ti,kw,tn,rn OR desametone:ab,ti,kw,tn,rn OR desigdron:ab,ti,kw,tn,rn OR 'dexa cortisyl':ab,ti,kw,tn,rn OR 'dexa dabrosan':ab,ti,kw,tn,rn OR 'dexa korti':ab,ti,kw,tn,rn OR 'dexa scherosan':ab,ti,kw,tn,rn OR 'dexa scherozon':ab,ti,kw,tn,rn OR 'dexa scherozone':ab,ti,kw,tn,rn OR 'dexa-p':ab,ti,kw,tn,rn OR 'dexacen 4':ab,ti,kw,tn,rn OR dexachel:ab,ti,kw,tn,rn OR dexacort:ab,ti,kw,tn,rn OR dexacortal:ab,ti,kw,tn,rn OR dexacorten:ab,ti,kw,tn,rn OR dexacortin:ab,ti,kw,tn,rn OR dexacortisyl:ab,ti,kw,tn,rn OR dexadabroson:ab,ti,kw,tn,rn OR dexadecadrol:ab,ti,kw,tn,rn OR dexadrol:ab,ti,kw,tn,rn OR dexagel:ab,ti,kw,tn,rn OR dexagen:ab,ti,kw,tn,rn OR dexahelvacort:ab,ti,kw,tn,rn OR dexakorti:ab,ti,kw,tn,rn OR dexalien:ab,ti,kw,tn,rn OR dexalocal:ab,ti,kw,tn,rn OR dexame:ab,ti,kw,tn,rn OR dexamecortin:ab,ti,kw,tn,rn OR dexameson:ab,ti,kw,tn,rn OR dexamesone:ab,ti,kw,tn,rn OR dexametason:ab,ti,kw,tn,rn OR dexametasone:ab,ti,kw,tn,rn OR dexameth:ab,ti,kw,tn,rn OR dexamethason:ab,ti,kw,tn,rn OR dexamethazon:ab,ti,kw,tn,rn OR dexamethazone:ab,ti,kw,tn,rn OR dexamethonium:ab,ti,kw,tn,rn OR dexamonozon:ab,ti,kw,tn,rn OR dexan:ab,ti,kw,tn,rn OR dexane:ab,ti,kw,tn,rn OR dexano:ab,ti,kw,tn,rn OR dexapot:ab,ti,kw,tn,rn OR dexascheroson:ab,ti,kw,tn,rn OR dexascherozon:ab,ti,kw,tn,rn OR dexascherozone:ab,ti,kw,tn,rn OR dexason:ab,ti,kw,tn,rn OR dexasone:ab,ti,kw,tn,rn OR dexinoral:ab,ti,kw,tn,rn OR dexionil:ab,ti,kw,tn,rn OR dexmethsone:ab,ti,kw,tn,rn OR dexona:ab,ti,kw,tn,rn OR dexone:ab,ti,kw,tn,rn OR dexpak:ab,ti,kw,tn,rn OR dextelan:ab,ti,kw,tn,rn OR dextenza:ab,ti,kw,tn,rn OR dextrasone:ab,ti,kw,tn,rn OR dexycu:ab,ti,kw,tn,rn OR dezone:ab,ti,kw,tn,rn OR dibasona:ab,ti,kw,tn,rn OR doxamethasone:ab,ti,kw,tn,rn OR esacortene:ab,ti,kw,tn,rn OR 'ex s1':ab,ti,kw,tn,rn OR exadion:ab,ti,kw,tn,rn OR exadione:ab,ti,kw,tn,rn OR firmalone:ab,ti,kw,tn,rn OR 'fluormethyl prednisolone':ab,ti,kw,tn,rn OR fluormethylprednisolon:ab,ti,kw,tn,rn OR fluormethylprednisolone:ab,ti,kw,tn,rn OR fluormone:ab,ti,kw,tn,rn OR fluorocort:ab,ti,kw,tn,rn OR fluorodelta:ab,ti,kw,tn,rn OR fluoromethylprednisolone:ab,ti,kw,tn,rn OR fortecortin:ab,ti,kw,tn,rn OR gammacorten:ab,ti,kw,tn,rn OR gammacortene:ab,ti,kw,tn,rn OR grosodexon:ab,ti,kw,tn,rn OR grosodexone:ab,ti,kw,tn,rn OR hemady:ab,ti,kw,tn,rn OR hexadecadiol:ab,ti,kw,tn,rn OR hexadecadrol:ab,ti,kw,tn,rn OR hexadiol:ab,ti,kw,tn,rn OR hexadrol:ab,ti,kw,tn,rn OR isnacort:ab,ti,kw,tn,rn OR 'isopto dex':ab,ti,kw,tn,rn OR 'isopto maxidex':ab,ti,kw,tn,rn OR 'isopto-dex':ab,ti,kw,tn,rn OR 'isopto-maxidex':ab,ti,kw,tn,rn OR isoptodex:ab,ti,kw,tn,rn OR isoptomaxidex:ab,ti,kw,tn,rn OR 'lokalison f':ab,ti,kw,tn,rn OR loverine:ab,ti,kw,tn,rn OR luxazone:ab,ti,kw,tn,rn OR marvidione:ab,ti,kw,tn,rn OR maxidex:ab,ti,kw,tn,rn OR mediamethasone:ab,ti,kw,tn,rn OR megacortin:ab,ti,kw,tn,rn OR mephameson:ab,ti,kw,tn,rn OR mephamesone:ab,ti,kw,tn,rn OR metasolon:ab,ti,kw,tn,rn OR metasolone:ab,ti,kw,tn,rn OR 'methazon ion':ab,ti,kw,tn,rn OR 'methazone ion':ab,ti,kw,tn,rn OR methazonion:ab,ti,kw,tn,rn OR methazonione:ab,ti,kw,tn,rn OR methylfluorprednisolone:ab,ti,kw,tn,rn OR 'metisone lafi':ab,ti,kw,tn,rn OR mexasone:ab,ti,kw,tn,rn OR millicorten:ab,ti,kw,tn,rn OR millicortenol:ab,ti,kw,tn,rn OR 'mk 125':ab,ti,kw,tn,rn OR mk125:ab,ti,kw,tn,rn OR mymethasone:ab,ti,kw,tn,rn OR neoforderx:ab,ti,kw,tn,rn OR neofordex:ab,ti,kw,tn,rn OR nisomethasona:ab,ti,kw,tn,rn OR novocort:ab,ti,kw,tn,rn OR 'nsc 34521':ab,ti,kw,tn,rn OR nsc34521:ab,ti,kw,tn,rn OR 'oftan-dexa':ab,ti,kw,tn,rn OR opticorten:ab,ti,kw,tn,rn OR opticortinol:ab,ti,kw,tn,rn OR oradexan:ab,ti,kw,tn,rn OR oradexon:ab,ti,kw,tn,rn OR oradexone:ab,ti,kw,tn,rn OR orgadrone:ab,ti,kw,tn,rn OR ozurdex:ab,ti,kw,tn,rn OR pidexon:ab,ti,kw,tn,rn OR policort:ab,ti,kw,tn,rn OR posurdex:ab,ti,kw,tn,rn OR 'predni f tablinen':ab,ti,kw,tn,rn OR 'predni-f':ab,ti,kw,tn,rn OR 'prednisolone f':ab,ti,kw,tn,rn OR prodexona:ab,ti,kw,tn,rn OR prodexone:ab,ti,kw,tn,rn OR sanamethasone:ab,ti,kw,tn,rn OR santenson:ab,ti,kw,tn,rn OR santeson:ab,ti,kw,tn,rn OR sawasone:ab,ti,kw,tn,rn OR solurex:ab,ti,kw,tn,rn OR spoloven:ab,ti,kw,tn,rn OR sterasone:ab,ti,kw,tn,rn OR thilodexine:ab,ti,kw,tn,rn OR triamcimetil:ab,ti,kw,tn,rn OR vexamet:ab,ti,kw,tn,rn OR visumetazone:ab,ti,kw,tn,rn OR visumethazone:ab,ti,kw,tn,rn OR '50-02-2':ab,ti,kw,tn,rn
#67 'difluprednate'/exp
#68 difluprednate*:ab,ti,kw,tn,rn OR 'cm 9155':ab,ti,kw,tn,rn OR cm9155:ab,ti,kw,tn,rn OR durezol:ab,ti,kw,tn,rn OR epitopic:ab,ti,kw,tn,rn OR myser:ab,ti,kw,tn,rn OR 'w 6309':ab,ti,kw,tn,rn OR w6309:ab,ti,kw,tn,rn OR 'warner 6309':ab,ti,kw,tn,rn OR env905:ab,ti,kw,tn,rn OR '23674-86-4':ab,ti,kw,tn,rn
#69 'fluorometholone'/exp
#70 ((fluorometholone*:ab,ti,kw,tn,rn OR cortilet:ab,ti,kw,tn,rn OR cortisdin:ab,ti,kw,tn,rn OR delmeson:ab,ti,kw,tn,rn OR delmesone:ab,ti,kw,tn,rn OR efflumidex:ab,ti,kw,tn,rn OR eflone:ab,ti,kw,tn,rn OR flosef:ab,ti,kw,tn,rn OR fluaton:ab,ti,kw,tn,rn OR flucon:ab,ti,kw,tn,rn OR fluforte:ab,ti,kw,tn,rn) AND liquifilm:ab,ti,kw,tn,rn OR flulon:ab,ti,kw,tn,rn OR flumelon:ab,ti,kw,tn,rn OR flumetholon:ab,ti,kw,tn,rn OR flumetholone:ab,ti,kw,tn,rn OR flumex:ab,ti,kw,tn,rn OR flumexo:ab,ti,kw,tn,rn OR fluometholone:ab,ti,kw,tn,rn OR fluoph:ab,ti,kw,tn,rn OR 'fluoro ophtal':ab,ti,kw,tn,rn OR 'fluor-op':ab,ti,kw,tn,rn OR fluorlon:ab,ti,kw,tn,rn OR fluormetholon:ab,ti,kw,tn,rn OR fluoromethalone:ab,ti,kw,tn,rn OR fluoropos:ab,ti,kw,tn,rn OR fml:ab,ti,kw,tn,rn OR fuluson:ab,ti,kw,tn,rn OR isopto:ab,ti,kw,tn,rn) AND flucon:ab,ti,kw,tn,rn OR loticort:ab,ti,kw,tn,rn OR methasite:ab,ti,kw,tn,rn OR oxylone:ab,ti,kw,tn,rn OR '426-13-1':ab,ti,kw,tn,rn
#71 'loteprednol etabonate'/exp
#72 loteprednol*:ab,ti,kw,tn,rn OR alrex:ab,ti,kw,tn,rn OR 'cddd 5604':ab,ti,kw,tn,rn OR cddd5604:ab,ti,kw,tn,rn OR cehoac:ab,ti,kw,tn,rn OR 'chloromethyl 17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate':ab,ti,kw,tn,rn OR '17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate, chloromethyl':ab,ti,kw,tn,rn OR 'chloromethyl 17 ethoxycarbonyloxy 11 hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate':ab,ti,kw,tn,rn OR eysuvis:ab,ti,kw,tn,rn OR 'hgp 1':ab,ti,kw,tn,rn OR hgp1:ab,ti,kw,tn,rn OR inveltys:ab,ti,kw,tn,rn OR 'kpi 121':ab,ti,kw,tn,rn OR kpi121:ab,ti,kw,tn,rn OR 'le-mpp':ab,ti,kw,tn,rn OR

lotemax:ab,ti,kw,tn,rn OR loterex:ab,ti,kw,tn,rn OR loterox:ab,ti,kw,tn,rn OR lotesoft:ab,ti,kw,tn,rn OR 'p 5604':ab,ti,kw,tn,rn OR p5604:ab,ti,kw,tn,rn OR '82034-46-6':ab,ti,kw,tn,rn
#73 'prednisolone'/exp
#74 prednisolone*:ab,ti,kw,tn,rn OR adelcort:ab,ti,kw,tn,rn OR antisolon:ab,ti,kw,tn,rn OR antisolone:ab,ti,kw,tn,rn OR aprednislon:ab,ti,kw,tn,rn OR aprednislone:ab,ti,kw,tn,rn OR benisolon:ab,ti,kw,tn,rn OR benisolone:ab,ti,kw,tn,rn OR berisolon:ab,ti,kw,tn,rn OR berisolone:ab,ti,kw,tn,rn OR caberdelta:ab,ti,kw,tn,rn OR capsoid:ab,ti,kw,tn,rn OR 'co hydeltra':ab,ti,kw,tn,rn OR codelcortone:ab,ti,kw,tn,rn OR compresolon:ab,ti,kw,tn,rn OR cortadeltona:ab,ti,kw,tn,rn OR cortadeltone:ab,ti,kw,tn,rn OR cortalone:ab,ti,kw,tn,rn OR cortelinter:ab,ti,kw,tn,rn OR cortisolone:ab,ti,kw,tn,rn OR cotolone:ab,ti,kw,tn,rn OR dacortin:ab,ti,kw,tn,rn OR dacrotin:ab,ti,kw,tn,rn OR decaprednil:ab,ti,kw,tn,rn OR 'decortin h':ab,ti,kw,tn,rn OR decortril:ab,ti,kw,tn,rn OR 'dehydro cortex':ab,ti,kw,tn,rn OR 'dehydro hydrocortisone':ab,ti,kw,tn,rn OR dehydrocortex:ab,ti,kw,tn,rn OR dehydrocortisol:ab,ti,kw,tn,rn OR dehydrocortisole:ab,ti,kw,tn,rn OR dehydrohydrocortison:ab,ti,kw,tn,rn OR dehydrohydrocortisone:ab,ti,kw,tn,rn OR delcortol:ab,ti,kw,tn,rn OR 'delta 1 17 hydroxycorticosterone 21 acetate':ab,ti,kw,tn,rn OR 'delta 1 hydrocortisone':ab,ti,kw,tn,rn OR 'delta cortef':ab,ti,kw,tn,rn OR 'delta cortril':ab,ti,kw,tn,rn OR 'delta ef cortelan':ab,ti,kw,tn,rn OR 'delta f':ab,ti,kw,tn,rn OR 'delta hycortol':ab,ti,kw,tn,rn OR 'delta hydrocortisone':ab,ti,kw,tn,rn OR 'delta ophticor':ab,ti,kw,tn,rn OR 'delta stab':ab,ti,kw,tn,rn OR 'delta-cortef':ab,ti,kw,tn,rn OR 'delta1 dehydrocortisol':ab,ti,kw,tn,rn OR 'delta1 dehydrohydrocortisone':ab,ti,kw,tn,rn OR 'delta1 hydrocortisone':ab,ti,kw,tn,rn OR deltacortef:ab,ti,kw,tn,rn OR deltacortenolo:ab,ti,kw,tn,rn OR deltacortil:ab,ti,kw,tn,rn OR deltacortoil:ab,ti,kw,tn,rn OR deltacortril:ab,ti,kw,tn,rn OR deltaderm:ab,ti,kw,tn,rn OR deltaglycortril:ab,ti,kw,tn,rn OR deltahycortol:ab,ti,kw,tn,rn OR deltahydrocortison:ab,ti,kw,tn,rn OR deltahydrocortisone:ab,ti,kw,tn,rn OR deltaophticor:ab,ti,kw,tn,rn OR deltasolone:ab,ti,kw,tn,rn OR deltastab:ab,ti,kw,tn,rn OR deltidrosol:ab,ti,kw,tn,rn OR deltisilone:ab,ti,kw,tn,rn OR deltisolon:ab,ti,kw,tn,rn OR deltisolone:ab,ti,kw,tn,rn OR deltolasson:ab,ti,kw,tn,rn OR deltolassone:ab,ti,kw,tn,rn OR deltosona:ab,ti,kw,tn,rn OR deltosone:ab,ti,kw,tn,rn OR 'depo-predate':ab,ti,kw,tn,rn OR dermosolon:ab,ti,kw,tn,rn OR dhasolone:ab,ti,kw,tn,rn OR diadresonf:ab,ti,kw,tn,rn OR 'di adreson f':ab,ti,kw,tn,rn OR 'di adresone f':ab,ti,kw,tn,rn OR 'di-adreson-f':ab,ti,kw,tn,rn OR 'diadreson f':ab,ti,kw,tn,rn OR 'diadresone f':ab,ti,kw,tn,rn OR dicortol:ab,ti,kw,tn,rn OR domucortone:ab,ti,kw,tn,rn OR encortelon:ab,ti,kw,tn,rn OR encortelone:ab,ti,kw,tn,rn OR encortolon:ab,ti,kw,tn,rn OR equisolon:ab,ti,kw,tn,rn OR 'fernisolone-p':ab,ti,kw,tn,rn OR glistelone:ab,ti,kw,tn,rn OR hefasolon:ab,ti,kw,tn,rn OR 'hostacortin h':ab,ti,kw,tn,rn OR hydeltra:ab,ti,kw,tn,rn OR hydeltrone:ab,ti,kw,tn,rn OR hydrelta:ab,ti,kw,tn,rn OR hydrocortancyl:ab,ti,kw,tn,rn OR hydrocortidelt:ab,ti,kw,tn,rn OR hydrodeltalone:ab,ti,kw,tn,rn OR hydrodeltisone:ab,ti,kw,tn,rn OR hydroretrocortin:ab,ti,kw,tn,rn OR hydroretrocortine:ab,ti,kw,tn,rn OR inflanefran:ab,ti,kw,tn,rn OR insolone:ab,ti,kw,tn,rn OR 'keteocort h':ab,ti,kw,tn,rn OR 'key-pred':ab,ti,kw,tn,rn OR lenisolone:ab,ti,kw,tn,rn OR leocortol:ab,ti,kw,tn,rn OR liquipred:ab,ti,kw,tn,rn OR 'lygal kopftinktur n':ab,ti,kw,tn,rn OR mediasolone:ab,ti,kw,tn,rn OR meprisolon:ab,ti,kw,tn,rn OR meprisolone:ab,ti,kw,tn,rn OR metacortalon:ab,ti,kw,tn,rn OR metacortalone:ab,ti,kw,tn,rn OR metacortandralon:ab,ti,kw,tn,rn OR metacortandralone:ab,ti,kw,tn,rn OR metacortelone:ab,ti,kw,tn,rn OR 'meti derm':ab,ti,kw,tn,rn OR meticortelone:ab,ti,kw,tn,rn OR metiderm:ab,ti,kw,tn,rn OR morlone:ab,ti,kw,tn,rn OR mydrapred:ab,ti,kw,tn,rn OR 'neo delta':ab,ti,kw,tn,rn OR nisolon:ab,ti,kw,tn,rn OR nisolone:ab,ti,kw,tn,rn OR 'nsc 9120':ab,ti,kw,tn,rn OR nsc9120:ab,ti,kw,tn,rn OR opredsone:ab,ti,kw,tn,rn OR panafcortelone:ab,ti,kw,tn,rn OR panafcortolone:ab,ti,kw,tn,rn OR panafort:ab,ti,kw,tn,rn OR paracortol:ab,ti,kw,tn,rn OR phlogex:ab,ti,kw,tn,rn OR 'pre cortisyl':ab,ti,kw,tn,rn OR preconin:ab,ti,kw,tn,rn OR precortalon:ab,ti,kw,tn,rn OR precortancyl:ab,ti,kw,tn,rn OR precortisyl:ab,ti,kw,tn,rn OR 'pred-ject-50':ab,ti,kw,tn,rn OR 'predacort 50':ab,ti,kw,tn,rn OR 'predaject-50':ab,ti,kw,tn,rn OR 'predalone 50':ab,ti,kw,tn,rn OR predartrina:ab,ti,kw,tn,rn OR predartrine:ab,ti,kw,tn,rn OR predate:ab,ti,kw,tn,rn OR 'predate-50':ab,ti,kw,tn,rn OR predeltilone:ab,ti,kw,tn,rn OR predisole:ab,ti,kw,tn,rn OR predisyr:ab,ti,kw,tn,rn OR 'predne dome':ab,ti,kw,tn,rn OR prednecort:ab,ti,kw,tn,rn OR prednedome:ab,ti,kw,tn,rn OR prednelan:ab,ti,kw,tn,rn OR 'predni coelin':ab,ti,kw,tn,rn OR 'predni h tablinen':ab,ti,kw,tn,rn OR 'predni-helvacort':ab,ti,kw,tn,rn OR prednicoelin:ab,ti,kw,tn,rn OR prednicort:ab,ti,kw,tn,rn OR prednicortelone:ab,ti,kw,tn,rn OR 'prednifor drops':ab,ti,kw,tn,rn OR predniment:ab,ti,kw,tn,rn OR predniretard:ab,ti,kw,tn,rn OR prednis:ab,ti,kw,tn,rn OR prednisil:ab,ti,kw,tn,rn OR prednisolon:ab,ti,kw,tn,rn OR prednisolona:ab,ti,kw,tn,rn OR prednivet:ab,ti,kw,tn,rn OR prednorsolon:ab,ti,kw,tn,rn OR prednorsolone:ab,ti,kw,tn,rn OR predonine:ab,ti,kw,tn,rn OR predorgasolona:ab,ti,kw,tn,rn OR predorgasolone:ab,ti,kw,tn,rn OR 'pregna 1, 4 diene 11beta, 17alpha, 21 triol 3, 20 dione':ab,ti,kw,tn,rn OR prelon:ab,ti,kw,tn,rn OR prelone:ab,ti,kw,tn,rn OR prenilone:ab,ti,kw,tn,rn OR prenin:ab,ti,kw,tn,rn OR prenolone:ab,ti,kw,tn,rn OR preventan:ab,ti,kw,tn,rn OR prezolon:ab,ti,kw,tn,rn OR rubycort:ab,ti,kw,tn,rn OR scherisolon:ab,ti,kw,tn,rn OR scherisolona:ab,ti,kw,tn,rn OR serilone:ab,ti,kw,tn,rn OR solondo:ab,ti,kw,tn,rn OR solone:ab,ti,kw,tn,rn OR solupren:ab,ti,kw,tn,rn OR soluprene:ab,ti,kw,tn,rn OR spiricort:ab,ti,kw,tn,rn OR spolotane:ab,ti,kw,tn,rn OR sterane:ab,ti,kw,tn,rn OR sterolone:ab,ti,kw,tn,rn OR supercortisol:ab,ti,kw,tn,rn OR supercortizol:ab,ti,kw,tn,rn OR taracortelone:ab,ti,kw,tn,rn OR walesolone:ab,ti,kw,tn,rn OR wysolone:ab,ti,kw,tn,rn OR '50-24-8':ab,ti,kw,tn,rn
#75 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74
#76 #58 AND #75
#77 #32 AND #76

## Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#2 dry[tw] AND (eye[tw] OR eyes[tw] OR eyelid*[tw]) NOT Medline[sb]
#3 (ocular[tw] AND dry[tw]) NOT Medline[sb]
#4 tear*[tw] NOT Medline[sb]
#5 xerophthalmi*[tw] NOT Medline[sb]

#6 ("vitamin A"[tw] AND deficien*[tw]) NOT Medline[sb]
#7 ("avitaminosis a"[tw] OR retinol deficien*[tw] OR "hypovitaminosis A"[tw]) NOT Medline[sb]
#8 (Keratoconjunctiv*[tw] OR "kerato conjunctivitis"[tw]) NOT Medline[sb]
#9 ((Sjogren*[tw] OR Sjoegren*[tw]) AND (syndrom*[tw] OR disease[tw] OR diseases[tw])) NOT Medline[sb]
#10 sicca syndrom*[tw] NOT Medline[sb]
#11 (Steven*[tw] AND Johnson[tw] AND (syndrom*[tw] OR disease[tw] OR diseases[tw])) NOT Medline[sb]
#12 (Cicatricial [tw] AND Pemphigoid*[tw]) NOT Medline[sb]
#13 Blepharoconjunctiviti*[tw] NOT Medline[sb]
#14 (meibomian[tw] OR tarsal[tw]) NOT Medline[sb]
#15 (lacrima*[tw] OR epiphora[tw]) NOT Medline[sb]
#16 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 corticosteroid*[tw] OR glucocorticoid*[tw] OR mineralocorticoid*[tw] OR "adrenal cortex hormone"[tw] OR "adrenal cortex hormones"[tw] OR "adrenal cortical hormone"[tw] OR "adrenal cortical hormones"[tw] OR "adrenocortical hormone"[tw] OR "adrenocortical hormones"[tw] OR adrenocorticosteroid*[tw] OR corticoid*[tw] OR steroid*[tw]
#18 Betamethasone*[tw] OR adbeon[tw] OR becasone[tw] OR beprogel[tw] OR "beta methason"[tw] OR "beta methasone"[tw] OR "beta-phos/ac"[tw] OR betacortril[tw] OR betadexamethasone[tw] OR betamethasone[tw] OR betamethasolone[tw] OR betamethasone[tw] OR betamethasonum[tw] OR betamethasone[tw] OR betason[tw] OR betnasol[tw] OR betnelan[tw] OR "betnesol v"[tw] OR "betnovate a"[tw] OR betsolan[tw] OR betsolon[tw] OR betsopart[tw] OR celestan[tw] OR celestene[tw] OR celeston[tw] OR celestona[tw] OR celestone[tw] OR cellestoderm[tw] OR cidoten[tw] OR dermobet[tw] OR diprolen[tw] OR flubenisolone[tw] OR methasone[tw] OR "nsc 39470"[tw] OR nsc39470[tw] OR ophtamesone[tw] OR "rg 833"[tw] OR rg833[tw] OR rinderon[tw] OR "sch 4831"[tw] OR sch4831[tw] OR walacort[tw] OR "378-44-9"[tw]
#19 "clobetasone butyrate"[tw] OR "cci 5537"[tw] OR cci5537[tw] OR "clobetasone 17 butyrate"[tw] OR emovate[tw] OR eumovate[tw] OR "gr 2 1214"[tw] OR "gr 2-1214"[tw] OR "gr 21214"[tw] OR "gr2-1214"[tw] OR kindavate[tw] OR "sn 203"[tw] OR sn203[tw] OR trimovate[tw] OR "25122-57-0"[tw]
#20 Dexamethasone*[tw] OR adrecort[tw] OR adrenocot[tw] OR "aeroseb dex"[tw] OR "aeroseb-d"[tw] OR aflucoson[tw] OR aflucosone[tw] OR alfalyl[tw] OR anaflogistico[tw] OR aphtasolon[tw] OR arcodexan[tw] OR arcodexane[tw] OR artrosone[tw] OR auxiron[tw] OR azium[tw] OR bidexol[tw] OR "bisu ds"[tw] OR calonat[tw] OR cebedex[tw] OR cetadexon[tw] OR colofoam[tw] OR corsona[tw] OR corsone[tw] OR cortastat[tw] OR cortidex[tw] OR cortidexason[tw] OR cortidrona[tw] OR cortidrone[tw] OR cortisumman[tw] OR "dacortina fuerte"[tw] OR "dacortine fuerte"[tw] OR dalalone[tw] OR danasone[tw] OR "de-sone la"[tw] OR decacortin[tw] OR decadeltosona[tw] OR decadeltosone[tw] OR decaderm[tw] OR decadion[tw] OR decadran[tw] OR decadron[tw] OR decadronal[tw] OR decadrone[tw] OR decaesadril[tw] OR decagel[tw] OR decaject[tw] OR decalix[tw] OR decameth[tw] OR decamethasone[tw] OR decasone[tw] OR decaspray[tw] OR decasterolone[tw] OR decdan[tw] OR decilone[tw] OR decofluor[tw] OR dectancyl[tw] OR dekacort[tw] OR delladec[tw] OR deltafluoren[tw] OR deltafluorene[tw] OR dergramin[tw] OR deronil[tw] OR desacort[tw] OR desacortone[tw] OR desadrene[tw] OR desalark[tw] OR desameton[tw] OR desametone[tw] OR desigdron[tw] OR "dexa cortisyl"[tw] OR "dexa dabrosan"[tw] OR "dexa korti"[tw] OR "dexa scherosan"[tw] OR "dexa scherozon"[tw] OR "dexa scherozone"[tw] OR "dexa-p"[tw] OR "dexacen 4"[tw] OR dexachel[tw] OR dexacort[tw] OR dexacortal[tw] OR dexacorten[tw] OR dexacortin[tw] OR dexacortisyl[tw] OR dexadabroson[tw] OR dexadecadrol[tw] OR dexadrol[tw] OR dexagel[tw] OR dexagen[tw] OR dexahelvacort[tw] OR dexakorti[tw] OR dexalien[tw] OR dexalocal[tw] OR dexame[tw] OR dexamecortin[tw] OR dexameson[tw] OR dexamesone[tw] OR dexametason[tw] OR dexametasone[tw] OR dexameth[tw] OR dexamethason[tw] OR dexamethazon[tw] OR dexamethazone[tw] OR dexamethonium[tw] OR dexamonozon[tw] OR dexan[tw] OR dexane[tw] OR dexano[tw] OR dexapot[tw] OR dexascheroson[tw] OR dexascherozon[tw] OR dexascherozone[tw] OR dexason[tw] OR dexasone[tw] OR dexinoral[tw] OR dexionil[tw] OR dexmethsone[tw] OR dexona[tw] OR dexone[tw] OR dexpak[tw] OR dextelan[tw] OR dextenza[tw] OR dextrasone[tw] OR dexycu[tw] OR dezone[tw] OR dibasona[tw] OR doxamethasone[tw] OR esacortene[tw] OR "ex s1"[tw] OR exadion[tw] OR exadione[tw] OR firmalone[tw] OR "fluormethyl prednisolone"[tw] OR fluormethylprednisolon[tw] OR fluormethylprednisolone[tw] OR fluormone[tw] OR fluorocort[tw] OR fluorodelta[tw] OR fluoromethylprednisolone[tw] OR fortecortin[tw] OR gammacorten[tw] OR gammacortene[tw] OR grosodexon[tw] OR grosodexone[tw] OR hemady[tw] OR hexadecadiol[tw] OR hexadecadrol[tw] OR hexadiol[tw] OR hexadrol[tw] OR isnacort[tw] OR "isopto dex"[tw] OR "isopto maxidex"[tw] OR "isopto-dex"[tw] OR "isopto-maxidex"[tw] OR isoptodex[tw] OR isoptomaxidex[tw] OR "lokalison f"[tw] OR loverine[tw] OR luxazone[tw] OR marvidione[tw] OR maxidex[tw] OR mediamethasone[tw] OR megacortin[tw] OR mephameson[tw] OR mephamesone[tw] OR metasolon[tw] OR metasolone[tw] OR "methazon ion"[tw] OR "methazone ion"[tw] OR methazonion[tw] OR methazonione[tw] OR methylfluorprednisolone[tw] OR "metisone lafi"[tw] OR mexasone[tw] OR millicorten[tw] OR millicortenol[tw] OR "mk 125"[tw] OR mk125[tw] OR mymethasone[tw] OR neoforderx[tw] OR neofordex[tw] OR nisomethasona[tw] OR novocort[tw] OR "nsc 34521"[tw] OR nsc34521[tw] OR "oftan-dexa"[tw] OR opticorten[tw] OR opticortinol[tw] OR oradexan[tw] OR oradexon[tw] OR oradexone[tw] OR orgadrone[tw] OR ozurdex[tw] OR pidexon[tw] OR policort[tw] OR posurdex[tw] OR "predni f tablinen"[tw] OR "predni-f"[tw] OR "prednisolone f"[tw] OR prodexona[tw] OR prodexone[tw] OR sanamethasone[tw] OR santenson[tw] OR santeson[tw] OR sawasone[tw] OR solurex[tw] OR spoloven[tw] OR sterasone[tw] OR thilodexine[tw] OR triamcimetil[tw] OR vexamet[tw] OR visumetazone[tw] OR visumethazone[tw] OR "50-02-2"[tw]
#21 difluprednate*[tw] OR "cm 9155"[tw] OR cm9155[tw] OR durezol[tw] OR epitopic[tw] OR myser[tw] OR "w 6309"[tw] OR w6309[tw] OR "warner 6309"[tw] OR ENV905[tw] OR "23674-86-4"[tw]
#22 Fluorometholone[tw]* OR cortilet[tw] OR cortisdin[tw] OR delmeson[tw] OR delmesone[tw] OR efflumidex[tw] OR eflone[tw] OR flosef[tw] OR fluaton[tw] OR flucon[tw] OR "fluforte liquifilm"[tw] OR flulon[tw] OR flumelon[tw] OR flumetholon[tw] OR flumetholone[tw] OR flumex[tw] OR flumexo[tw] OR fluometholone[tw] OR fluoph[tw] OR "fluoro ophtal"[tw] OR "fluor-op"[tw] OR fluorlon[tw] OR

fluormetholon[tw] OR fluoromethalone[tw] OR fluoropos[tw] OR fml[tw] OR fuluson[tw] OR "isopto flucon"[tw] OR loticort[tw] OR methasite[tw] OR oxylone[tw] OR "426-13-1"[tw]
#23 Loteprednol*[tw] OR alrex[tw] OR "cddd 5604"[tw] OR cddd5604[tw] OR CEHOAC[tw] OR "Chloromethyl 17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate"[tw] OR "17-ethoxycarbonyloxy-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylate, Chloromethyl"[tw] OR "Chloromethyl 17 ethoxycarbonyloxy 11 hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate"[tw] OR eysuvis[tw] OR "hgp 1"[tw] OR hgp1[tw] OR inveltys[tw] OR "kpi 121"[tw] OR kpi121[tw] OR "le-mpp"[tw] OR lotemax[tw] OR loterex[tw] OR loterox[tw] OR lotesoft[tw] OR "p 5604"[tw] OR p5604[tw] OR "82034-46-6"[tw]
#24 Prednisolone*[tw] OR adelcort[tw] OR antisolon[tw] OR antisolone[tw] OR aprednislon[tw] OR aprednislone[tw] OR benisolon[tw] OR benisolone[tw] OR berisolon[tw] OR berisolone[tw] OR caberdelta[tw] OR capsoid[tw] OR "co hydeltra"[tw] OR codelcortone[tw] OR compresolon[tw] OR cortadeltona[tw] OR cortadeltone[tw] OR cortalone[tw] OR cortelinter[tw] OR cortisolone[tw] OR cotolone[tw] OR dacortin[tw] OR dacrotin[tw] OR decaprednil[tw] OR "decortin h"[tw] OR decortril[tw] OR "dehydro cortex"[tw] OR "dehydro hydrocortisone"[tw] OR "dehydro hydrocortisone"[tw] OR dehydrocortex[tw] OR dehydrocortisol[tw] OR dehydrocortisole[tw] OR dehydrohydrocortison[tw] OR dehydrohydrocortisone[tw] OR delcortol[tw] OR "delta 1 17 hydroxycorticosterone 21 acetate"[tw] OR "delta 1 hydrocortisone"[tw] OR "delta cortef"[tw] OR "delta cortril"[tw] OR "delta ef cortelan"[tw] OR "delta f"[tw] OR "delta hycortol"[tw] OR "delta hydrocortisone"[tw] OR "delta hydrocortisone"[tw] OR "delta ophticor"[tw] OR "delta stab"[tw] OR "delta-cortef"[tw] OR "delta1 dehydrocortisol"[tw] OR "delta1 dehydrohydrocortisone"[tw] OR "delta1 hydrocortisone"[tw] OR deltacortef[tw] OR deltacortenolo[tw] OR deltacortil[tw] OR deltacortoil[tw] OR deltacortril[tw] OR deltaderm[tw] OR deltaglycortril[tw] OR deltahycortol[tw] OR deltahydrocortison[tw] OR deltahydrocortisone[tw] OR deltaophticor[tw] OR deltasolone[tw] OR deltastab[tw] OR deltidrosol[tw] OR deltisilone[tw] OR deltisolon[tw] OR deltisolone[tw] OR deltolasson[tw] OR deltolassone[tw] OR deltosona[tw] OR deltosone[tw] OR "depo-predate"[tw] OR dermosolon[tw] OR dhasolone[tw] OR DiAdresonF[tw] OR "di adreson f"[tw] OR "di adresone f"[tw] OR "di-adreson-f"[tw] OR "diadreson f"[tw] OR "diadresone f"[tw] OR dicortol[tw] OR domucortone[tw] OR encortelon[tw] OR encortelone[tw] OR encortolon[tw] OR equisolon[tw] OR "fernisolone-p"[tw] OR glistelone[tw] OR hefasolon[tw] OR "hostacortin h"[tw] OR hydeltra[tw] OR hydeltrone[tw] OR hydrelta[tw] OR hydrocortancyl[tw] OR hydrocortidelt[tw] OR hydrodeltalone[tw] OR hydrodeltisone[tw] OR hydroretrocortin[tw] OR hydroretrocortine[tw] OR inflanefran[tw] OR insolone[tw] OR "keteocort h"[tw] OR "key-pred"[tw] OR lenisolone[tw] OR leocortol[tw] OR liquipred[tw] OR "lygal kopftinktur n"[tw] OR mediasolone[tw] OR meprisolon[tw] OR meprisolone[tw] OR metacortalon[tw] OR metacortalone[tw] OR metacortandralon[tw] OR metacortandralone[tw] OR metacortelone[tw] OR "meti derm"[tw] OR meticortelone[tw] OR metiderm[tw] OR morlone[tw] OR mydrapred[tw] OR "neo delta"[tw] OR nisolon[tw] OR nisolone[tw] OR "nsc 9120"[tw] OR nsc9120[tw] OR opredsone[tw] OR panafcortelone[tw] OR panafcortolone[tw] OR panafort[tw] OR paracortol[tw] OR phlogex[tw] OR "pre cortisyl"[tw] OR preconin[tw] OR precortalon[tw] OR precortancyl[tw] OR precortisyl[tw] OR "pred-ject-50"[tw] OR "predacort 50"[tw] OR "predaject-50"[tw] OR "predalone 50"[tw] OR predartrina[tw] OR predartrine[tw] OR predate[tw] OR "predate-50"[tw] OR predeltilone[tw] OR predisole[tw] OR predisyr[tw] OR "predne dome"[tw] OR prednecort[tw] OR prednedome[tw] OR prednelan[tw] OR "predni coelin"[tw] OR "predni h tablinen"[tw] OR "predni-helvacort"[tw] OR prednicoelin[tw] OR prednicort[tw] OR prednicortelone[tw] OR "prednifor drops"[tw] OR predniment[tw] OR predniretard[tw] OR prednis[tw] OR prednisil[tw] OR prednisolon[tw] OR prednisolona[tw] OR prednivet[tw] OR prednorsolon[tw] OR prednorsolone[tw] OR predonine[tw] OR predorgasolona[tw] OR predorgasolone[tw] OR "pregna 1, 4 diene 11beta, 17alpha, 21 triol 3, 20 dione"[tw] OR prelon[tw] OR prelone[tw] OR prenilone[tw] OR prenin[tw] OR prenolone[tw] OR preventan[tw] OR prezolon[tw] OR rubycort[tw] OR scherisolon[tw] OR scherisolona[tw] OR serilone[tw] OR solondo[tw] OR solone[tw] OR solupren[tw] OR soluprene[tw] OR spiricort[tw] OR spolotane[tw] OR sterane[tw] OR sterolone[tw] OR supercortisol[tw] OR supercortizol[tw] OR taracortelone[tw] OR walesolone[tw] OR wysolone[tw] OR "50-24-8"[tw]
#25 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26 #1 AND #16 AND #25

## Appendix 5. LILACS search strategy

("Dry Eye" OR "Síndromes de Ojo Seco" OR "Síndromes do Olho Seco" OR MH:C11.496.260$ OR Tear$ OR Lágrimas OR MH:A12.200.882$ OR Xerophthalmia OR Xeroftalmia OR MH:C11.187.810$ OR MH:C11.496.260.892$ OR "Vitamin A Deficiency" OR "Deficiencia de Vitamina A" OR MH:C18.654.521.500.133.628$ OR MH:SP6.016.052.063.109$ OR "avitaminosis a" OR "retinol deficiency" OR "hypovitaminosis A" OR Keratoconjunctivitis OR " kerato conjunctivitis" OR Queratoconjuntivitis OR Ceratoconjuntivite OR MH:C11.187.183.394$ OR MH:C11.204.564.585$ OR MH:C11.496.260.394$ OR "Sjogren's Syndrome" OR "Síndrome de Sjögren" OR MH:C05.550.114.154.774$ OR MH:C05.799.114.774$ OR MH:C07.465.815.929.669$ OR MH:C11.496.260.719$ OR MH:C17.300.775.099.774$ OR MH:C20.111.199.774$ OR "sicca syndrome" OR "Stevens Johnson Syndrome" OR "Síndrome de Stevens Johnson" OR MH:C07.465.864.500$ OR MH:C17.800.229.400.683$ OR MH:C17.800.865.475.683$ OR "Pemphigoid Benign Mucous Membrane" OR "Penfigoide Benigno de la Membrana Mucosa" OR "Penfigoide Mucomembranoso Benigno" OR "Cicatricial Pemphigoid" OR MH:C11.187.482$ OR MH:C17.800.865.670$ OR blepharoconjunctiviti$ OR "Meibomian Glands" OR "Glándulas Tarsales" OR "Glândulas Tarsais" OR MH:A09.371.337.614 OR MH:A10.336.827.600 OR "Lacrimal Apparatus Diseases" OR "Enfermedades del Aparato Lagrimal" OR "Doenças do Aparelho Lacrimal" OR MH:C11.496$ OR lacrima$ or epiphora) AND (corticosteroid$ OR glucocorticoid$ OR mineralocorticoid$ OR "adrenal cortex hormone" OR "adrenal cortical hormone" OR "adrenocortical hormone" OR adrenocorticosteroid$ OR corticoid$ OR steroid$ OR MH:D06.472.040$ OR Betamethason$ OR Betametason$ OR MH:4.210.500.745.432.769.199$ OR MH:D04.210.500.908.093$ OR "Clobetasone butyrate" OR Dexamethason$ OR Dexametason$ OR MH:D04.210.500.745.432.769.344$ OR MH:D04.210.500.908.238$ OR Difluprednat$ OR Fluorometholon$ OR MH:D04.210.500.745.432.719.349$ OR MH:D04.210.500.908.431$ OR "Loteprednol etabonate" OR MH:D04.210.500.054.079.129.284$ OR "Etabonato de Loteprednol" OR Prednisolon$ OR MH:D04.210.500.745.432.769.795$)

### Appendix 6. ClinicalTrials.gov search strategy

(dry eye OR Keratoconjunctivitis) AND (corticosteroid OR glucocorticoid OR mineralocorticoid OR adrenal cortex hormones OR adrenal cortical hormones OR adrenocortical hormones OR adrenocorticosteroid OR corticoid OR steroids OR betamethasone OR clobetasone butyrate OR dexamethasone OR difluprednate OR fluorometholone OR loteprednol etabonate OR prednisolone)

### Appendix 7. WHO ICTRP search strategy

dry eye AND corticosteroid OR dry eye AND glucocorticoid OR dry eye AND mineralocorticoid OR dry eye AND adrenal cortex hormones OR dry eye AND adrenal cortical hormones OR dry eye AND adrenocortical hormones OR dry eye AND adrenocorticosteroid OR dry eye AND corticoid OR dry eye AND steroids OR dry eye AND betamethasone OR dry eye AND clobetasone butyrate OR dry eye AND dexamethasone OR dry eye AND difluprednate OR dry eye AND fluorometholone OR dry eye AND loteprednol etabonate OR dry eye AND prednisolone

Keratoconjunctivitis AND corticosteroid OR Keratoconjunctivitis AND glucocorticoid OR Keratoconjunctivitis AND mineralocorticoid OR Keratoconjunctivitis AND adrenal cortex hormones OR Keratoconjunctivitis AND adrenal cortical hormones OR Keratoconjunctivitis AND adrenocortical hormones OR Keratoconjunctivitis AND adrenocorticosteroid OR Keratoconjunctivitis AND corticoid OR Keratoconjunctivitis AND steroids OR Keratoconjunctivitis AND betamethasone OR Keratoconjunctivitis AND clobetasone butyrate OR Keratoconjunctivitis AND dexamethasone OR Keratoconjunctivitis AND difluprednate OR Keratoconjunctivitis AND fluorometholone OR Keratoconjunctivitis AND loteprednol etabonate OR Keratoconjunctivitis AND prednisolone

## HISTORY

Protocol first published: Issue 9, 2021

## CONTRIBUTIONS OF AUTHORS

All review authors contributed to the conception and design of the study, participated in study selection, data extraction, and/or analysis, drafted portions of the review, commented on drafts critically regarding intellectual content, and approved the final version for publication.

## DECLARATIONS OF INTEREST

- **Su-Hsun Liu:** reports a grant from the National Eye Institute, National Institutes of Health, USA; payment to institution.
- **Ian J Saldanha:** reports grants and contracts, Cochrane Eyes and Vision, from National Eye Institute, National Institutes of Health, USA; payment to institution. Travel reimbursement for making a talk on outcomes related to dry eye in 2018 from Johns Hopkins Wilmer Eye Institute; personal payment.
- **Alison G Abraham:** declared that she has no conflicts of interest.
- **Thanitsara Rittiphairoj:** declared that she has no conflicts of interest.
- **Scott Hauswirth:** reports grants and contracts for paid investigator from TearSolutions and Sylentis (contract pending—study not yet underway as of 23 February 2021); paid to institution. Payments for presentations from Kala Pharmaceuticals, Dompe, Sun Pharmaceuticals, Takeda, and Avedro; personal payment. Support for INTREPID meeting (indirect) from Alcon/Novartis; personal payment. Stock shares in Oyster Point (paid for and owned individually, not as compensation), TearRestore (compensation for design and medical advisory work), and Horizon Pharma (paid for and owned individually, not as compensation); personal payment. Consulting fees for study design and analysis from Ocular Therapeutix (pending); personal payment. Advisory Board payments from Dompe, NuSight Medical, Kala Pharmaceuticals, Sun Pharmaceuticals, EyePoint Medical, EyeVance Pharma, Horizon Pharma, Avedro/Glaukos, Quidel, and Sight Sciences; personal payment. Writing assistance from Takeda (medical writer for review paper); personal payment. SH reports publishing opinions on topical immunomodulation in dry eye in the OSDocs Facebook group (moderator/co-administrator role), and published 'When dry eye compromises corneal integrity' in *Review of Optometry*, Nov 2017 (contract pending—study not yet underway as of 23 February 2021). They report working as an Optometrist at the University of Colorado.
- **Darren Gregory:** reports working as an Ophthalmologist at the University of Colorado Eye Center. Their clinical work focuses on the treatment of dry eyes, which sometimes involves the use of topical corticosteroid medications.
- **Cristos Ifantides:** reports being an inventor with intellectual property assigned to their university. The design relates to dry eye, but does not relate to corticosteroid use for dry eye. It is a design for a new form of eyeglasses that can theoretically help with dry eye (patent application filed, University of Colorado), paid to institution. Ownership of stock in Pfizer. Their partner works for AbbVie, which makes medications related to dry eye. She does not work in the eye care space. CI reports working as a clinician at Denver Health and University of Colorado, where they are an attending physician.
- **Tianjing Li:** reports a grant from the National Eye Institute, National Institutes of Health, USA; payment to institution.

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- Queen's University Belfast, UK

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We excluded trials that compared topical corticosteroid therapy, alone or in combination therapy, with the following comparator therapy: (1) intense pulsed light therapy; (2) steroid iontophoresis or inserts; (3) herbal medicines; these comparators were not specifically listed in the protocol.
2. For trials that randomized participants but reported outcome data for both eyes without specifying which eye was the study eye, we extracted and analyzed data for the right eye. We did not define this lateral preference in the protocol.
3. We did not perform planned subgroup analysis by sex because the included trials did not report sex-specific symptom scores or corneal staining results.
4. We did not perform subgroup analysis on one of the critical outcomes, tear film break-up time, by etiology as planned in the protocol because fewer than 10 studies reported this outcome for either comparison. Instead, we chose to perform subgroup analysis on one of the important outcomes, fluorescein corneal staining scores, by etiology.
5. For the subjective and objective outcomes that we chose for risk of bias assessment, we also performed post hoc subgroup analysis by questionnaire or scale, source of funding, and intervention regimen (steroid type, duration).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects]; Cataract [drug therapy]; Cyclosporine [adverse effects]; *Dry Eye Syndromes [drug therapy]; *Glucocorticoids [adverse effects]; Loteprednol Etabonate; Lubricant Eye Drops; Randomized Controlled Trials as Topic; Tobramycin

### MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Male