Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Targeted Drugs for Dry Eye Disease

Date of Review: June 2025 **End Date of Literature Search:** 02/26/2025

Purpose for Class Review:
The purpose of this review is to evaluate the evidence related to the treatment of dry eye, which is currently unfunded. A medical necessity pathway for coverage for Early and Periodic Screening, Diagnostic, and Treatment (EPSTD) patients will be created, which can be expanded to additional populations in 2027 when the Oregon Health Plan (OHP) prioritized list is retired.

Plain Language Summary:
- Dry eye disease is a common eye condition associated with eye pain and trouble seeing. Dry eye is currently not a funded treatment for Oregon Health Plan members. Prescription dry eye therapies are available for patients who qualify through the Early and Periodic Screening, Diagnostic, and Treatment (EPSTD) program.
- Artificial tears, also known as lubricants, are available without a prescription. Artificial tears are recommended to help the initial symptoms of dry eye.
- If artificial tears fail to provide relief of symptoms, prescription products are available to treat the symptoms associated with dry eye. Prescription dry eye drops are cyclosporine, loteprednol, lifitegrast and perfluorohexyloctane. Varenicline nasal spray is a prescription used to improve dry eye symptoms.
- Randomized controlled trials, systematic reviews, and meta-analyses provide evidence that Food and Drug Administration (FDA) approved products for dry are more effective than placebo (an inactive product) for improving dry eye symptoms.
- Guidelines recommend treating dry eye disease with artificial tears as an initial option and using prescription products if symptoms of dry eye continue.
- The Drug Use Research and Management Group recommends that artificial tears be used for patients with dry eye. If bothersome symptoms persist, and the member qualifies under EPSDT, then prescription products for dry eye should be covered after going through the prior authorization process.

Research Questions:
1. What is the new comparative evidence for efficacy and effectiveness for certain drugs used for dry eye disease for outcomes such as symptom improvement?
2. What is the evidence for safety associated with certain drugs used for dry eye (e.g., burning or pain at instillation site)?
3. Are there subpopulations in which certain dry eye treatments are associated with more benefit or more harm?

Conclusions:
- In this review there were 2 new systematic reviews and meta-analyses, 2 new guidelines, and 7 randomized controlled trials (RCTs) identified.
- A Cochrane review found topical steroids to have lower scores (which is favored) in patient reported symptom scores (measured by the Ocular Surface Disease Index [OSDI] or Visual Analog Scale, 0-100 points) than artificial tears (AT) in patients with dry eye moderate evidence (standard mean difference [SMD] -0.29; 95% confidence interval [CI], -0.42 to -0.16; moderate evidence). A change of 0.2 is representative of a small difference which may not be

clinically significant.[1] Tear film break up time (TBUT) was longer with steroids compared to AT based on low quality of evidence. The TBUT is used to measure the time the tear film on the eye surface remains stable before breaking up, shorter lengths of time are indicative of dry eye (10 seconds or less). The change in TBUT was considered clinically meaningful (mean difference [MD] 7.0 sec; 95% CI, 0.06 to 1.34) with a minimal clinically significant change of 5 sec with steroids compared to AT.[1] Low-quality evidence found greater reductions in patient reported symptoms in those treated with steroids compared to cyclosporin (CSA) (standard mean difference [SMD] -0.33; 95% CI, -0.51 to -0.15).[1]

- The use of CSA, in combination with AT, was more effective for reducing the signs and symptoms of dry eye at 6 months compared to AT alone based on a Cochrane review (low-quality evidence).[2] The evidence on tear production and stability was inconsistent.[2]
- The American Academy of Ophthalmology (AAO) guidance on the treatment of dry eye disease recommends ocular lubricants (i.e., artificial tears) first-line for dry eye (high-quality evidence).[3] Prescription products are considered second-line with no preference of one therapy over another.
- The National Institute for Health and Care Excellence (NICE) recommends the use of CSA as an option for adult patients with dry eye and severe keratitis that does not improve with the use of AT.[4]
- Seven randomized clinical trials compared the efficacy and safety of the following dry eye therapies compared to vehicle or saline: lifitigrast[5–7], CSA[8], perfluorohexyloctane[9,10] and varenicline[11]. Active treatments were more effective at reporting patient symptom compared to control.
- There was insufficient evidence to suggest that there are certain subpopulations who would benefit more or less from certain therapies for dry eye.
- There is also a pathway for coverage for the treatment of vernal keratoconjunctivitis as CSA products are used for this indication.

Recommendations:

- Create a PDL class for prescription drugs used for dry eye. Make all prescription products for the treatment of dry eye and vernal keratoconjunctivitis nonpreferred based on the evidence.
- No changes in coverage for over-the-counter artificial tear products.
- Implement prior authorization (PA) criteria to provide a pathway for coverage for therapies for vernal keratoconjunctivitis and for dry eye therapies for patients with comorbidities which allow for funding of dry eye or who qualify under EPSTD (**Appendix 6**).
- Evaluate costs in executive session.

Background:

Dry eye syndrome, also known as dry eye disease or keratoconjuctivitis, is a common eye ailment diagnosed upon clinical examination. It occurs in 5% to 50% of the population, depending on study population and diagnostic criteria.[2] A recent systematic review and meta-analysis reports an incidence of 3.5% in those 18 years and older and 7.8% in adults 68 years and older.[12] Common symptoms of dry eye are discomfort and visual disability, such as blurred vision and inability to read or drive. Burning, photophobia and dryness may also be present.[2] Dry eye is the result of the inability of the lacrimal functional unit (lacrimal glands, ocular surface and lids, and the sensory and motor nerves) to maintain a stable precorneal tear layer.[2] Ocular inflammation is thought to be a key component of dry eye.[1] Causes of dry eye can be due to aging, inflammation, cataract or refractive surgery, diabetes, Sjögren's syndrome, thyroid eye disease, or secondary to ocular diseases such as glaucoma.[2] The most common risk factor is age and it is more common in women compared to men.[2] Additional risk factors are contact lens wear, screen time, androgen deficiency and medication use (i.e., diuretics, anxiolytics, nonsteroidal anti-inflammatory drugs [NSAIDs], antipsychotics, inhaled steroids and antidepressants).[13]

There is no one test used to diagnose dry eye and clinical examination is the standard of care for diagnosis.[3] Types of dry eye include aqueous-deficient dry eye, evaporative dry eye, and mixed mechanism of both types. Tear supplements and tear stimulants for tear preservation are recommended for aqueous-deficient

dry eye.[1] There is a lack of evidence to recommend punctal plugs or autologous serum eye drops.[1] The treatment of evaporated dry eye treatment is guided by underlying cause, with the use of topical steroids and cyclosporine recommended for ocular surface inflammation.[1]

Therapies to treat dry eye consists of procedural and pharmacotherapy. Long-term treatment is often necessary, as most treatments are for symptomatic improvements compared to curative.[3] Clinical assessment of treatment efficacy is most often determined by symptom improvement in response to therapy. Over the counter ocular lubricants (i.e., artificial tears) can be helpful in the management of dry eye, and are available in liquid, gel and ointment formulations. Non-preserved tear substitutes are recommended if patients require administration of 4 times a day or more, as excessive exposure to preservatives can cause toxic conjuctivitis.[14] Persistent symptoms may require additional treatment. Prescription drugs FDA-approved for the treatment of dry eye include topical products: loteprednol, lifitegrast, cyclosporine, and perfluorohexyloctane (**Table 1).** Varenicline nasal spray is the only nasal treatment approved for dry eye. Approved treatments for dry eye have different mechanisms and there is no guidance on comparative efficacy of prescription products.[13] Cyclosporine is an immunomodulatory therapy that prevents activation and function of T lymphocytes.[2] In some cases, topical CSA may lead to long-term remission in symptoms.[3] Topical steroids are often used for the short-term (up to 1 month) treatment of dry eye. Topical steroids have a rapid onset of action making them a pre-treatment option before using long-term treatments such as CSA.[1] Topical lifitegrast is an integrin antagonist that has evidence of improving signs and symptoms of dry eye in patients with mild to severe symptoms. Safety of use beyond 12 months is uknown.[3] Intranasal varenicline, a nicotinic acetylcholine receptor agonist, stimulates natural tear production. Perfluorohexyloctane is a tear substitute drop demonstrating improvement in the signs and symptoms of dry eye. Topical products take between 1-3 months after initiation to alleviate symptoms; however, CSA treatment effects may take longer.[15]

For patients with severe dry eye, such as those with Sjögren's syndrome, a cholinergic agonist may be appropriate. Drugs approved for this indication include the cholinergic agonists, pilocarpine and cevimeline. Adverse effects include excessive sweating and ocular irritation.[3] For patients with blepharitis, including meibomian gland dysfunction, the use of oral tetracycline or doxycycline for 2-4 weeks or oral azithromycin for 5 days may be effective for the treatment of dry eye.[14]

Patients with vernal keratoconjunctivitis (VK) may also be prescribed CSA products, in which topical doses with concentrations of 0.1% or greater may be an effective treatment for this condition.[16] The brand name CSA product, VERKAZIA, is specifically approved for VK. Vernal keratoconjunctivitis is inflammation of conjunctiva usually occurring in children and young adults, ages 5-25 years, in hot, dry climates such as Middle East, Mediterranean basin, North and West Africa, parts of India, Central America and South America.[16] Other medications besides topical CSA for VK include mast cell stabilizers, antihistamines, NSAIDs, and topical corticosteroids (short-term).[16] There are no direct comparison studies evaluating treatments for VK.

The most common adverse reactions associated with the use of prescription dry eye products include instillation site pain and blurred vision. Patients prescribed corticosteroids should be monitored for adverse events such as increased intraocular pressure and cataract formation.[3]

Important outcomes in the treatment of dry eye are general symptom improvement, including relief of eye discomfort, dryness, and visual impairment. There is not a gold standard for symptom assessment. The OSDI is a validated questionnaire used for evaluation of dry eye symptoms. It includes 12 questions to determine the severity of dry eye.[13] Total score ranges from 0-100 points with higher scores indicating greater disability. The minimal clinically important difference (MCID) for OSDI is 4.5 to 7.3 units for mild to moderate dry eye and 7.3-13.4 units for severe dry eye.[17] The Dry Eye Questionnaire-5 (DEQ-5) focuses on degree of eye discomfort, dryness and wateriness by rating severity on a 0 (never) to 4 (constantly) scale. A score of 6 or more is considered positive for the diagnosis of dry eye.[18] The Visual Analog Scale (VAS) is also used to rank severity of symptoms, with a change in symptom severity score of at least 30% considered a clinically significant change. The Schirmer tear test measures the rate of tear production in the eye and is used in the diagnosis of dry eye.

Fluorescein staining scores can also assist in the diagnosis of dry eye by highlighting areas of damage on the ocular surface. The National Eye Institute Grading Scale is often used.[19] Scores are graded from 0 to 3, with a 0 indicating no staining and 3 indicating severe eye staining. A score higher than 0 is abnormal.

There was only one claim for loteprednol in Q3 of 2024 quarter most likely for an indication other than dry eye. Dry eye currently falls below the funding line so there is no utilization for the other products.

A summary of relevant drug information is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. FDA-approved Drugs for Dry Eye Disease Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Loteprednol 0.25% suspension (EYSUVIS)[20]	• Indicated for the short-term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease	• Topical	1-2 drops into each eye four times daily
Lifitegrast 5% solution (XIIDRA)[21]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop twice daily in each eye approximately 12 hours apart.
Cyclosporine 0.05% emulsion (RESTASIS)[22]	• To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.	• Topical	One drop twice a day in each eye approximately 12 hours apart.
Cyclosporine 0.09% solution (CEQUA)[23]	• To increase tear production in patients with keratoconjunctivitis sicca (dry eye)	• Topical	One drop twice daily approximately 12 hours apart into each eye. Discard the vial immediately after using in both eyes.
Cyclosporine 0.1% emulsion (VERKAZIA)[24]	• For the treatment of vernal keratoconjunctivitis (seasonal eye irritation) in children and adults	• Topical	One drop, 4 times daily (morning, noon, afternoon and evening) in each affected eye
Cyclosporine 0.1% solution (VEVYE)[25]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop twice a day in each eye approximately 12 hours apart
Varenicline nasal spray (TYRVAYA)[26]	• For the treatment of the signs and symptoms of dry eye disease	• Nasal	One spray in each nostril twice daily approximately 12 hours apart
Perfluorohexyloctane solution (MIEBO)[27]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop four times a day

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Cochrane – Topical Corticosteroids for Dry Eye
A Cochrane systematic review and meta-analysis evaluated treatment of dry eye.[1] The literature was searched up to August of 2021. Randomized controlled trials of ophthalmic topical steroids (as monotherapy or in combination with tobramycin) were compared to no treatment, AT, inert vehicles , AT plus tobramycin or CSA. Topical steroids used in the studies were clobetasone, difluprednate, loteprednol etabonate, fluorometholone, methylprednisolone and corticosteroid. There were 22 RCTs identified for inclusion. All but one trial included adults 18 years and older.[1] Females accounted for 79% of the population.[1] Most trials were small, enrolling 40-158 participants. Topical steroid use ranged from 1 week to 3 months.[1] Five trials included patients with Sjögren's syndrome. Almost half of the trials were at high risk of bias due to selective outcome reporting.

Topical steroids, with or without tobramycin, were compared to eye lubricants (e.g., hyaluronate, soothe emollient or polyvinylpyrrolidone), vehicle, no treatment or AT in 15 studies. There was moderate strength of evidence that the change in patient-reported symptom scores were lower in those treated with topical steroids compared to AT (SMD -0.29; 95% CI, -0.42 to -0.16).[1] Tear film break up time was longer in the steroid treated group compared to AT, suggesting benefit with steroids (MD 0.70; 95% CI, 0.06 to 1.34) (low quality of evidence).[1] Lower fluorescein corneal staining scores were present in those treated with steroids compared to AT (SMD -0.40; 95% CI, -0.62 to -0.18) (moderate quality of evidence). Steroids, compared to AT, were associated with elevated intraocular pressure but evidence was considered very low.

Steroids (e.g., fluorometholone, loteprednol, or methylprednisolone) alone, or in combination with CSA, were compared to CSA. Symptom scores were lower in patients treated with steroids compared to CSA (SMD -0.33; 95% CI, -0.51 to -0.15) based on low quality evidence.[1] Changes of 0.2 were considered small; therefore, unlikely to be clinically significant. A moderate change would be 0.5 in symptom scores. Changes in TBUT were longer in those treated with steroids compared to CSA based on low quality evidence (MD 0.37 sec; 95% CI, -0.13 to 0.87); however, changes were not statistically significant.[1] Changes in fluorescein corneal staining scores were higher in the steroid group suggesting that treatment with CSA was favored (SMD 0.05; 95% CI, -0.25 to 0.35; p>0.05) (low quality of evidence).[1] There was very low evidence of increased intraocular pressure in those treated with steroids compared to CSA (relative risk [RR] 1.45; 95% CI, 0.25 to 8.33; p>0.05).[1]

Overall, topical steroids provide small to moderate relief of symptoms of dry eye compared to lubricants or CSA. Additional research is needed to determine the effects on tear film quality and quantity.

Cochrane – Topical Cyclosporine for Dry Eye Syndrome

In 2019 a systematic review and meta-analysis was conducted by Cochrane on the treatment of dry eye with topical CSA.[2] Thirty trials enrolling 4,009 patients were identified for inclusion. Trials lasted 6 weeks to 12 months. Trials studied the use of CSA compared to AT and CSA plus AT versus CSA alone. Concentrations of CSA were 0.05%, 0.1%, 1% and 2%.[2] A meta-analysis of all trial results was not possible due to lack of details results reporting.

A majority of trials (n=18) studied CSA 0.05% in combination with AT compared to a placebo vehicle and AT or AT monotherapy. All results for dry eye outcomes were based on low quality of evidence.[2] Symptom improvement at 6 months was reported by one, small (n=56) RCT and found CSA to be superior to comparator (MD -4.80; 95% CI, -6.41 to -3.19).[2] Ocular surface dye staining results at 6 months was not conclusive with 2 trials reporting results with inconsistent findings. Aqueous tear production (measured by Schirmer test scores) found CSA to be superior to comparators in one analysis (RR 3.50; 95% CI, 2.09 to 5.85) and improved, but not statistically so, in another analysis (RR 0.98; 95% CI, 0.83 to 1.17) (7 studies total).[2] Tear film stability at 6 months, measured by TBUT, was improved in those treated with CSA versus comparator with results ranging from 0.90 to 4.00. Conjunctival goblet cell density was higher in those treated with CSA compared to control with a MD of 22.5 cells per unit (95% CI, 16.3 to 28.8).[2] CSA was consistently associated with burning and stinging upon administration.

Additional comparisons studying different concentrations of CSA generally favored CSA over control; however, calculations on the differences were not able to be calculated due to lack of result reporting.

After review, one systematic review was excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[28]

Guidelines:

High Quality Guidelines:

American Academy of Ophthalmology – Dry Eye Syndrome Preferred Practice Patterns Guideline

The AAO updated previous guidance on the treatment of dry eye with a 2023 guideline.[3] Literature was searched on March 3, 2022 and June 7, 2023. Studies are rated using the SIGN scale from I++ to III (See **Appendix 1** for details). Recommendations are defined by GRADE as strong or discretionary.[3]

Ocular lubricants are offered as a Step 1 treatment for dry eye (I+, Good, Strong).[3] Non-preserved ocular lubricants can be tried as Step 2 therapy if ocular lubricants are inadequate. In Step 2 the following prescription drugs can be used to manage dry eye[3]:

- Topical antibiotic or antibiotic/steroid combination applied to the lid margin for anterior blepharitis.
- Topical corticosteroids (limited duration)
- Topical secretagogues
- Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics (used for meibomianitis and blepharitis)

If the above fail to control symptoms, then Step 3 recommends oral secretagogues, autologous/allogenic serum eye drops (I+, Moderate, Discretionary) and therapeutic contact lens as options (e.g., soft bandage lens and rigid scleral lenses).[3] In Step 4 for those without adequate relief from Steps 1-3 can consider:

topical corticosteroids for longer duration, amniotic membrane grafts, surgical punctal occlusion, or other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation).[3]

Limitations to the guideline include the lack of grading of all recommendations provided. Only select recommendations provided an evidence grade and strength of recommendation.

NICE – Cyclosporin for Treating Dry Eye

2015 NICE guidance focused on the use of CSA for people with dry eye that have not improved with AT.[4] Cyclosporin is recommended as an option for adults with dry eye with severe keratitis that has not improved with AT treatment.

Patients with Sjögren's syndrome and severe dry eye received the most benefit of CSA, with AT.[4] There was a lack of comparative evidence studying CSA compared to the established standard of care, corticosteroid and AT treatment. Eye pain, eye irritation, lacrimation, ocular hyperemia and eyelid erythema were noted common adverse reactions. There is no evidence of differences between CSA formulations due to lack of comparative data.[4]

Excluded Publications:

After review, 1 guideline was excluded due to poor quality.

The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS II) Management and Therapy Report was excluded due to poor quality, rigor of development and systematic approach.[29]

Randomized Controlled Trials:

A total of 125 citations were manually reviewed from the initial literature search. After further review, 118 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 7 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Akpek, et al[8] ESSENCE-2 DB, MC, PC Phase 3, RCT	1. Water-free CSA 0.1% solution (VEVYE) twice daily Vs. 2. Vehicle twice daily Trial duration = 29 days	Patients with moderate to severe dry eye N=834	Change from baseline in total corneal fluorescein staining (tCFS; score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -4.0 grades 2. -3.6 grades change -0.4 (95% CI, -0.8 to 0; p=0.03) Dryness score: 1. -12.2 2. -13.6 Change 1.4 (95% CI, -1.8 to 4.6 p=0.38)	Patients had to be using AT and dryness score of 50 or more for inclusion. Eye with highest baseline tCFS was designated the study eye. *Cyclosporine was more effective than placebo for tCFS scores but not for dryness scores.*

Holland, et al[7] OPUS-3 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 12 weeks	Patients with artificial tear use within the previous 30 days, corneal staining score of ≥2.0 (0-4 scale), STS >1 to <10 mm and eye dryness score of ≥40 (0-100 VAS) N=711	Change in eye dryness score (VAS in study eye) from baseline to day 84	Change in VAS: 1. -37 2. -29 TE 7.16 (95% CI, 3.04 to 11.28; P<0.0007)	Patients were an average of 58.7 years and 75.5% were female. Cataracts were present in 33.9% of patients. Fifty-eight percent of patients had a mean ICSS of 2.46 and mean eye dryness score of 68 at baseline indicating more severe dry eye. *Lifitegrast was more effective than placebo for changes in VAS.*
Sheppard, et al[9] MOJAVE DB, MC, PC (saline), Phase 3, RCT	1. Perfluorohexyloctane solution 1 drop 4 times daily Vs. 2. Hypotonic saline 0.6% 4 times daily Trial duration = 8 weeks	Adult patients with self-reported history of dry eye disease in both eyes that was verified by dry eye testing N=620	Change from baseline in tCFS (score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -2.3 grades 2. -1.1 grades MC -1.2 (95% CI, -1.7 to -0.8; p<0.001) Dryness score: 1. -29.4 2. -19.2 MD-10.2 (95% CI, -14.4 to -6.1 p<0.001)	Patients were mostly white females with a mean age of 54 years. Eye dryness at baseline was a mean of 64 suggestive of severe dry eyes. Hypotonic saline has been used in the treatment of dry eye. *Perfluorohexyloctane was more effective than placebo for tCFS scores and for dryness scores.*
Sheppard, et al[5] OPUS-1 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 84 days	Patients with bilateral dry eye disease N=588	Mean change from baseline ICSS at day 84 and mean change from baseline in the VR-OSDI†	Change in ICSS: 1. 0.16 2. -0.9 P=0.0007 Change in VR-OSDI was not significant (numerical results were not provided) P=0.7894	Fifty percent of patients had cataracts and 43% were using artificial tears. Lack of study details makes interpretation of results difficult. *Lifitegrast was more effective than placebo for changes in ICSS but not for changes in VR-OSDI.*

Tauber, et al[10] GOBI DB, MC, PC (saline), Phase 3, RCT	1. Perfluorohexyloctane solution 1 drop 4 times daily Vs. 2. Hypotonic saline 0.6% 4 times daily Trial duration = 8 weeks	Adult patients with self-reported history of dry eye disease in both eyes that was verified by dry eye testing N=599	Change from baseline in (tCFS; score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -2.0 grades 2. -1.0 grades LSMD -0.97 (95% CI, -1.4 to -0.55; p<0.001) Dryness score: 1. -27.4 2. -19.7 LSMD -7.6 (95% CI, -11.8 to -3.4 p<0.001)	Patients were mostly white females with a mean age of 61 years. Eye dryness at baseline was a mean of 67 suggestive of severe dry eyes. Hypotonic saline has been used in the treatment of dry eye. *Perfluorohexyloctane was more effective than placebo for tCFS scores and for dryness scores.*
Tauber, et al[6] OPUS-2 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 84 days	Patients with artificial tear use within the previous 30 days, inferior corneal staining score of ≥0.5 (0-4 scale), STS >1 to <10 mm and eye dryness score of >40 (0-100 VAS) N=718	Change in eye dryness score (VAS in both eyes) and change in ICSS in study eye	Change in VAS: 1. -35.30 2. -22.75 TE 12.61 (95% CI, 8.51 to 16.70; P<0.0001) Change in ICSS: 1. -0.71 2. -0.73 TE 0.03 (95% CI, -0.10 to 0.17; P=0.6186)	Cataracts were present in 35% of patients. Over 70% were female. Fifty-eight percent of patients had inferior corneal staining score or > 1.5 and eye dryness score of ≥60 at baseline indicating more severe dry eye. *Lifitegrast was more effective than placebo for changes in VAS but not for changes in ICSS.*
Wirta, et al ONSET-2 DB, MC, PC Phase 3, RCT	1. Varenicline 0.03 mg solution 1 spray twice daily intranasally 2. Varenicline 0.06 mg solution 1 spray twice daily intranasally Vs.	Adults 22 years and older with a diagnosis of dry eye disease, artificial tear use, ocular surface index score of 23 or more and STS	Percentage of patients achieving a 10-mm improvement or more in STS at week 4	1. 47.3% 2. 49.2% 3. 27.8% 1. vs. 3. OR 2.6 (95% CI, 1.7 to 3.8; p<0.0001; ARR 19.5/NNT 5) 2. vs. 3. OR 2.5 (95% CI, 1.7 to 3.6; p<0.0001; ARR 21.4/NNT 5)	Patients were an average of 58 years old and mostly White (83%) with moderate to severe dry eye. *Varenicline was more effective than placebo for the percent of patients with a clinically meaningful increase in STS (defined as an increase of at least 10 mm from baseline)*

	3. Vehicle 1 spray twice daily intranasally Trial duration = 4 weeks	of 10 mm or less N=758			

Key: * National Eye Institute Scale: scale ranges from 0 (no staining) to 3 (heavy staining) for 5 areas of the cornea. †The VR-OSDI measures ocular surface disease by accessing dry eye symptoms.
Abbreviations: ARR – absolute risk reduction; AT – artificial tears; CI - confidence interval; CSA – cyclosporine; DB - double-blind; ICSS - inferior corneal fluorescein staining score; LSMD – least square mean difference; MC – multi-center; MD – mean difference; NNT – number needed to treat; OR - odds ratio; PC – placebo-controlled; RCT – randomized controlled trial; STS - Schirmer test score; TE – treatment effect; tCFS - total corneal fluorescein staining; VAS – visual analog score; VR-OSDI- Visual-Related function subscale score of the Ocular Surface Disease Index.

References:

1. Liu SH, Saldanha IJ, Abraham AG, et al. Topical corticosteroids for dry eye. Cochrane Eyes and Vision Group, ed. *Cochrane Database of Systematic Reviews*. 2022;2022(10). doi:10.1002/14651858.CD015070.pub2

2. Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database of Systematic Reviews*. 2019;(9). doi:10.1002/14651858.CD010051.pub2

3. Amescua G, Ahmad S, Cheung AY, et al. American Academy of Opthalmology Dry Eye Syndrome Preferred Practice Pattern. *Ophalmology*. 2024 April;131(4):P1-49.

4. National Institute for Health and Care Excellence. Cyclosporin for Treating Dry Eye Disease that has not Improved Despite Treatmen with Artificial Tears. Technology Appraisal Guidance. 2015;December. Available at: www.nice.org.uk/guidance/ta369. Accessed March 1, 2025.

5. Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. *Ophthalmology*. 2014;121(2):475-483. doi:10.1016/j.ophtha.2013.09.015

6. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. *Ophthalmology*. 2015;122(12):2423-2431. doi:10.1016/j.ophtha.2015.08.001

7. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). *Ophthalmology*. 2017;124(1):53-60. doi:10.1016/j.ophtha.2016.09.025

8. Akpek EK, Sheppard JD, Hamm A, Angstmann-Mehr S, Krösser S. Efficacy of a new water-free topical cyclosporine 0.1% solution for optimizing the ocular surface in patients with dry eye and cataract. *J Cataract Refract Surg*. 2024;50(6):644-650. doi:10.1097/j.jcrs.0000000000001423

9. Sheppard JD, Kurata F, Epitropoulos AT, Krösser S, Vittitow JL. NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study. *American Journal of Ophthalmology*. 2023;252:265-274. doi:10.1016/j.ajo.2023.03.008

10. Tauber J, Berdy GJ, Wirta DL, et al. NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction. *Ophthalmology*. 2023;130(5):516-524. doi:10.1016/j.ophtha.2022.12.021

11. Wirta D, Vollmer P, Paauw J, et al. Efficacy and Safety of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease: The ONSET-2 Phase 3 Randomized Trial. *Ophthalmology*. 2022;129(4):379-387. doi:10.1016/j.ophtha.2021.11.004

12. McCann P, Abraham AG, Mukhopadhyay A, et al. Prevalence and Incidence of Dry Eye and Meibomian Gland Dysfunction in the United States: A Systematic Review and Meta-analysis. *JAMA Ophthalmology*. 2022;140(12):1181-1192. doi:10.1001/jamaophthalmol.2022.4394

13. Shtein R. Dry Eye Disease. *UpToDate*. 2024. August.

14. Hakim FE, Farooq AV. Dry Eye Disease: An Update in 2022. *JAMA*. 2022;327(5):478-479. doi:10.1001/jama.2021.19963

15. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II Report Executive Summary. *Ocul Surf*. 2017;15(4):802-812. doi:10.1016/j.jtos.2017.08.003

16. Randall, D. Vernal Keratoconjunctivitis. *DynaMed.* November 1, 2023. Available at: https://www-dynamed-com.liboff.ohsu.edu/condition/vernal-keratoconjunctivitis#GUID-F7D260F6-A5FF-4DB4-A4FC-F76A51F912A2. Accessed April 30th, 2025.

17. Miller K, Walt J,, Mink D, et al. Minimal Clinically Important Difference for the Ocular Surface Disease Index. *Arch Opthalmol*. 2010;128(1):94-101. doi:10.1001/archopthalmol.2009.356.

18. Robert MC, van Zuuren E, Grant A. Dry Eye Disease. *DynaMed*. 2024. June.

19. Sali K, Foulks G, Pucker A et al. Validation of a Modified National Eye Institute Grading Scale for Corneal Fluorescein Staining. *Dove Medical Press*. 2023;17:757-767.

20. Eyesuvis (loteprednol) [prescribing information]. Watertown, MA; Kala Pharmaceuticals, Inc. October 2020.

21. Xiidra (lifitegrast ophthalmic solution 5%) [prescribing information]. East Hanover, NJ; Novartis Pharmaceuticals Corporation. June 2020.

22. Restasis (cyclosporine ophthalmic emulsion 0.05%) [prescribing information]. Irvine, CA; Allergan, Inc. November 2012.

23. Cequa (cyclosporine ophthalmic solution 0.09%) [prescribing information]. Cranbury, NJ; Sun Pharmaceutical Industries, Inc. September 2019.

24. Verkazia (cyclosporine opthalmic emulsion .1%) [prescribing information]. Emeryville, CA; Santen Inc. June 2021.

25. Vevye (cyclosporine ophthalmic solution 0.1%) [prescribing information]. Nashville, TN. Harrow Eye, LLC. May 2024.

26. Tyrvaya (varenicline solution) [prescribing information]. Princeton, NJ; Oyster Point Pharma, Inc. February 2024.

27. Miebo (perfluorohexyloctane ophthalmic solution) [prescribing information]. Bridgewater, NJ; Bausch & Lomb Incorporated. May 2023.

28. Ballesteros-Sánchez A, Borroni D, De-Hita-Cantalejo C, et al. Efficacy of bilateral OC-01 (varenicline solution) nasal spray in alleviating signs and symptoms of dry eye disease: A systematic review. *Contact Lens and Anterior Eye*. 2024;47(1):102097. doi:10.1016/j.clae.2023.102097

29. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *The Ocular Surface*. 2017;15(3):575-628. doi:10.1016/j.jtos.2017.05.006

Appendix 1:

Evidence Grading for the Scottish Intercollegiate Guideline Network[3]:
I++: High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++: High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
II+: Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III: Nonanalytic studies (e.g., case reports, case series)

Appendix 2: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Cyclosporine ophthalmic solution 0.09% (CEQUA)[23]	Calcineurin inhibitor immunosuppressant agent thought to act as a partial immunomodulator when applied topically	Not detectable	NA	NA
Cyclosporine ophthalmic emulsion 0.05% (RESTASIS)[22]				
Cyclosporine ophthalmic solution 0.1% (VEVYE)[25]				
Lifitegrast ophthalmic solution 5% (XIIDRA)[21]	Lymphocyte function-associated antigen-1 (LFA-1) antagonist	Trough plasma concentrations ranged from 0.55 ng/mL to 3.74 ng/mL	NA	NA
Loteprednol ophthalmic solution 0.25% (EYESUVIS)[20]	Corticosteroid inhibition of inflammatory response thought to inhibit prostaglandin production	Below limit of quantitation in plasma	NA	NA
Perfluorohexyloctane ophthalmic solution (MIEBO)[27]	Semifluorinated alkane which creates a monolayer at the air-liquid interface of the tear film which reduces evaporation	Low systemic blood levels after topical administration	Not metabolized by liver microsomes in vitro	NA
Varenicline solution (TYRVAYA)[26]	Cholinergic agonist resulting in increased production of basal tear film	Systemic exposure following intranasal administration was approximately 7.5% of 1 mg oral dose of varenicline	Minimal metabolism with 92% excreted unchanged in the urine	Half-life = 19 hours ± 10 hours

Abbreviations: NA = not applicable

Use in Specific Populations:

Drug Safety:

Common adverse events are dependent upon class of drug, with the exception of preservatives. When preservatives are added to any product, they can cause eye irritation if used often. The most common adverse event for perfluorohexyloctane solution is blurred vision. This solution is preservative free. Varenicline is most associated with sneezing and cough. Instillation site reactions (e.g., pain and burning) are the most common side effect for CSA products. The most common adverse reaction occurring with lifitegrast are instillation-site irritation and decreased visual acuity. Loteprednol is associated with instillation site pain as the most common adverse reaction.

There are no warnings/precautions or contraindications for drugs used for dry eye unless described in **Table 4** below.

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Loteprednol suspension	Cyclosporine drops (RESTASIS)	Cyclosporine drops (VEVYE)	Lifitegrast solution
Delayed healing and corneal perforation	X			
Increase intraocular pressure	X			
Cataracts	X			
Bacterial infections	X			
Viral infections	X			
Fungal infections	X			
Do not touch vial tip to eye		X		
Contraindications	In patients with viral diseases of the cornea and conjunctiva and mycobacterial infection of the eye and fungal diseases of ocular structures	Hypersensitivity	None	Hypersensitivity

Appendix 3: Study Abstracts

Efficacy and Safety of a Water-Free Topical Cyclosporine, 0.1%, Solution for the Treatment of Moderate to Severe Dry Eye Disease: The ESSENCE-2 Randomized Clinical Trial

Esen K Akpek , David L Wirta , Johnathon E Downing, Joseph Tauber, John D Sheppard, Joseph B Ciolino, Alice S Meides, Sonja Krösser

Importance: Dry eye disease (DED) is a common public health problem with significant impact on vision-related quality of life and well-being of patients. Medications with rapid onset of action and a good tolerability profile remain an unmet need.
Objective: To assess efficacy, safety, and tolerability of a water-free cyclosporine ophthalmic solution, 0.1% (CyclASol [Novaliq GmbH]), applied twice daily in DED compared with vehicle.
Design, setting, and participants: CyclASol for the Treatment of Signs and Symptoms of Dry Eye Disease (ESSENCE-2) was a phase 3, multicenter, randomized, double-masked, vehicle-controlled clinical study conducted from December 5, 2020, to October 8, 2021. Following a 14-day run-in period with an artificial tear administered 2 times per day, eligible participants were randomly assigned 1:1 to the treatment groups. Patients with moderate to severe DED were included in the study.
Interventions: Cyclosporine solution vs vehicle administered 2 times per day for 29 days.
Main outcomes and measures: The primary end points were changes from baseline in total corneal fluorescein staining (tCFS; 0-15 National Eye Institute scale) and in dryness score (0-100 visual analog scale) at day 29. Conjunctival staining, central corneal fluorescein staining, and tCFS responders were also assessed.
Results: A total of 834 study participants were randomly assigned to cyclosporine (423 [50.7%]) or vehicle (411 [49.3%]) groups at 27 sites. Participants had a mean (SD) age of 57.1 (15.8) years, and 609 (73.0%) were female individuals. The majority of participants self-identified in the following race categories: 79 Asian (9.5 %), 108 Black (12.9%), and 635 White (76.1%). Participants treated with cyclosporine solution had greater improvement in tCFS (-4.0 grades) than the vehicle group (-3.6 grades) at day 29 (change [Δ] = -0.4; 95% CI, -0.8 to 0; P = .03). The dryness score showed treatment benefits from baseline in both groups: -12.2 points for cyclosporine and -13.6 points for vehicle (Δ = 1.4; 95% CI, -1.8 to 4.6; P = .38). In the cyclosporine group, 293 participants (71.6%) achieved clinically meaningful reductions of 3 grades or higher in tCFS vs 236 (59.7%) in the vehicle group (Δ = 12.6%; 95% CI, 6.0%-19.3%; P < .001). These responders showed greater improvement in symptoms at day 29 including dryness (Δ = -4.6; 95% CI, -8.0 to -1.2; P = .007) and blurred vision (Δ = -3.5; 95% CI, -6.6 to -4.0; P = .03) compared with nonresponders.
Conclusions and relevance: The ESSENCE-2 trial confirmed that treatment with a water-free cyclosporine solution, 0.1%, results in early therapeutic effects on the ocular surface compared with vehicle. The responder analyses suggest that the effect is clinically meaningful in 71.6% of participants in the cyclosporine group.

Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3)

Edward J Holland, Jodi Luchs, Paul M Karpecki, Kelly K Nichols, Mitchell A Jackson, Kenneth Sall, Joseph Tauber, Monica Roy, Aparna Raychaudhuri, Amir Shojaei

Purpose: Lifitegrast is a lymphocyte function-associated antigen-1 antagonist developed to reduce inflammation in dry eye disease (DED). We report the results of OPUS-3 (NCT02284516), a phase III study evaluating the efficacy and safety of lifitegrast versus placebo in participants with DED.
Design: Twelve-week, phase III, randomized, double-masked, multicenter, placebo-controlled study.
Participants: Adults aged ≥18 years with Schirmer tear test (without anesthesia) ≥1 and ≤10 mm, corneal fluorescein staining score ≥2.0 (0-4 scale), eye dryness score (EDS) ≥40 (0-100 visual analogue scale [VAS]), and history of artificial tear use within 30 days of study entry.
Methods: After a 14-day placebo run-in, participants were randomized 1:1 to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 84 days.

Main outcome measures: The primary efficacy end point was change from baseline to day 84 in EDS. Key secondary efficacy end points were change from baseline to days 42 and 14 in EDS. Other secondary efficacy end points included additional VAS items (burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain), ocular discomfort score (ODS), and safety/tolerability of lifitegrast versus placebo.
Results: In the study, 711 participants were randomized: placebo, 356; lifitegrast, 355 (intention-to-treat [ITT] population). At day 84, lifitegrast-treated participants experienced significantly greater improvement from baseline in EDS versus those receiving placebo (treatment effect [TE], 7.16; 95% confidence interval [CI], 3.04-11.28; P = 0.0007). Mean changes from baseline in EDS also significantly favored lifitegrast on days 42 (TE, 9.32; 95% CI, 5.44-13.20; P < 0.0001) and 14 (TE, 7.85; 95% CI, 4.33-11.37; P < 0.0001). No statistically significant differences were observed in ODS between treatment groups at days 84, 42, or 14. A greater improvement was observed in lifitegrast-treated participants at day 42 in itching (nominal P = 0.0318), foreign body sensation (nominal P = 0.0418), and eye discomfort (P = 0.0048) versus participants receiving placebo. Most treatment-emergent adverse events were mild to moderate in severity; no serious ocular adverse events were reported.
Conclusions: Lifitegrast significantly improved symptoms of eye dryness, as measured by EDS, versus placebo in participants with DED. Improvement in EDS was observed as early as day 14. Lifitegrast appeared well tolerated.

NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study
John D Sheppard, Fred Kurata, Alice T Epitropoulos, Sonja Krösser, Jason L Vittitow; MOJAVE Study Group

Purpose: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop for the treatment of signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD).
Design: Randomized, double-masked, controlled trial.
Methods: Patients ≥18 years of age with a history of DED and signs of MGD were randomly assigned 1:1 to treatment with NOV03 or hypotonic saline (0.6%) 4 times daily for 8 weeks. The primary sign and symptom endpoints were change from baseline to week 8 in total corneal fluorescein staining (tCFS; National Eye Institute scale) and eye dryness score (0-100 visual analog scale), respectively.
Results: A total of 620 patients (NOV03, n = 311; saline, n = 309) were randomized and treated. Least-squares (LS) mean change from baseline to week 8 was statistically significantly greater for NOV03 compared with saline for both tCFS (-2.3 vs -1.1; LS mean treatment difference, -1.2 [95% confidence interval -1.7 to -0.8]; P < .001) and visual analog scale dryness score (-29.4 vs -19.2; LS mean treatment difference, -10.2 [95% CI -14.4 to -6.1]; P < .001), with statistically significant between-group differences observed as early as week 2. The incidence of ocular adverse events was similar for NOV03 (12.9%) and saline (12.3%). There were no serious adverse events and no adverse events leading to treatment discontinuation.
Conclusions: In this randomized controlled trial of patients with DED associated with MGD, NOV03 significantly reduced both signs and symptoms of DED compared with hypotonic saline control. NOV03 was well tolerated, with an adverse event profile similar to that of saline.

Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study
John D Sheppard, Gail L Torkildsen, John D Lonsdale, Francis A D'Ambrosio Jr, Eugene B McLaurin, Richard A Eiferman, Kathryn S Kennedy, Charles P Semba; OPUS-1 Study Group

Purpose: To assess the efficacy and safety of lifitegrast ophthalmic solution 5.0% compared with placebo in subjects with dry eye disease.
Design: Prospective, randomized, double-masked, placebo-controlled, parallel arm, multicenter clinical trial.
Participants: A total of 588 adult subjects with dry eye disease.

Methods: Eligible subjects were randomized 1:1 to receive topically administered lifitegrast (5.0%) or placebo (vehicle) twice daily for 84 days after a 14-day open-label placebo run-in period. After enrollment (day 0), subjects were evaluated at days 14, 42, and 84. Key objective (fluorescein and lissamine staining scores [Ora scales]) and subjective (Ocular Surface Disease Index [OSDI], 7-item visual analog scale, and ocular discomfort score [Ora scale]) measures were assessed at all visits.
Main outcome measures: The primary objective efficacy measure (sign) was mean change from baseline inferior corneal staining score (ICSS) at day 84. The co-primary subjective efficacy measure (symptom) was the mean change from baseline in the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI). Supportive measures included corneal fluorescein scores (superior, central, total region) and conjunctival lissamine scores (nasal, temporal, total region) and symptom scores at day 84.
Results: The study met the primary objective efficacy ICSS end point in demonstrating superiority of lifitegrast compared with placebo (P = 0.0007). Lifitegrast significantly reduced corneal fluorescein staining (superior, P = 0.0392; total cornea, P = 0.0148) and conjunctival lissamine staining (nasal, P = 0.0039; total conjunctiva, P = 0.0086) at day 84 versus placebo. Significant (P < 0.05) improvements in nasal and total lissamine scores were observed at day 14 and maintained through day 84. The study did not meet the co-primary subjective VR-OSDI measure (P = 0.7894). However, significant improvements were observed at day 84 in ocular discomfort (P = 0.0273) and eye dryness (P = 0.0291), the most common and severe symptoms reported at baseline in both groups. There were no unanticipated or serious ocular adverse events (AEs). The most frequent reported ocular AEs were transient intermittent instillation site symptoms (irritation, discomfort) primarily on the initial lifitegrast dose at day 0.
Conclusions: Lifitegrast ophthalmic solution 5.0% significantly reduced corneal fluorescein and conjunctival lissamine staining and improved symptoms of ocular discomfort and eye dryness compared with placebo when administered twice daily over 84 days.

NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction: Results of the Randomized Phase 3 GOBI Study
Joseph Tauber, Gregg J Berdy, David L Wirta, Sonja Krösser, Jason L Vittitow; GOBI Study Group

Purpose: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop in patients with dry eye disease (DED) associated with meibomian gland dysfunction (MGD).
Design: Eight-week, phase 3, multicenter, randomized, double-masked, saline-controlled study.
Participants: Adults ≥ 18 years with a history of DED for ≥ 6 months, tear film breakup time of ≤ 5 seconds, Schirmer I test (without anesthesia) score ≥ 5 mm, MGD score ≥ 3 (0-15 scale), and total corneal fluorescein staining (tCFS) score ≥ 4 and ≤ 11 (0-15 National Eye Institute [NEI] scale).
Methods: Patients were randomized 1:1 to NOV03 or hypotonic (0.6%) saline 4 times daily.
Main outcome measures: The primary sign and symptom end points were change from baseline in tCFS and eye dryness score (0-100 visual analog scale [VAS]) at week 8. Key secondary end points were change from baseline in eye dryness score at week 2, tCFS at week 2, eye burning or stinging score (0-100 VAS) at week 8, and central corneal fluorescein staining (cCFS; 0-3 NEI scale) at week 8.
Results: Of the 599 patients randomized, 597 were treated (NOV03, n = 303; saline, n = 294). At week 8, improvement from baseline was significantly greater (P < 0.001) with NOV03 versus saline for tCFS (least square [LS] mean treatment difference, -0.97; 95% confidence interval [CI]: -1.40, -0.55) and VAS dryness score (-7.6; 95% CI: -11.8, -3.4). Improvement from baseline also significantly (P < 0.01) favored NOV03 on all key secondary end points: LS mean treatment difference (95% CI) was -4.7 (-8.2, -1.2) for VAS dryness score at week 2, -0.6 (-0.9, -0.2) for tCFS at week 2, -5.5 (-9.5, -1.6) for VAS burning or stinging score at week 8, and -0.2 (-0.4, -0.1) for cCFS at week 8. Most ocular adverse events (AEs) were mild in severity; no serious ocular AEs occurred. One patient discontinued NOV03 because of an AE (eye irritation).
Conclusions: In patients with DED associated with MGD, NOV03 demonstrated statistically significant and clinically meaningful improvements versus hypotonic saline in signs and symptoms of DED and was well tolerated.

Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study
Joseph Tauber, Paul Karpecki, Robert Latkany, Jodi Luchs, Joseph Martel, Kenneth Sall, Aparna Raychaudhuri, Valerie Smith, Charles P Semba; OPUS-2 Investigators

Purpose: Lifitegrast is an integrin antagonist that decreases T-cell-mediated inflammation associated with dry eye disease (DED). We report the results of OPUS-2, a phase III study evaluating the efficacy and safety of lifitegrast compared with placebo for the treatment of DED.
Design: A 12-week, multicenter, randomized, prospective, double-masked, placebo-controlled clinical trial.
Participants: Adults aged ≥18 years with use of artificial tears within 30 days, inferior corneal staining score ≥0.5 (0-4 scale), Schirmer tear test (without anesthesia) ≥1 and ≤10 mm, and eye dryness score ≥40 (0-100 visual analogue scale [VAS]).
Methods: Subjects were randomized 1:1 after 14-day placebo run-in to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 84 days.
Main outcome measures: Co-primary efficacy end points were change, from baseline to day 84, in eye dryness score (VAS, both eyes) and inferior corneal fluorescein staining score in the designated study eye. Secondary end points were change, from baseline to day 84, in ocular discomfort score (0-4 scale) in study eye, eye discomfort score (VAS), total corneal staining score in the study eye, and nasal conjunctival lissamine green staining score (0-4 scale) in the study eye. Treatment-emergent adverse events (TEAEs) were recorded.
Results: A total of 718 subjects were randomized: placebo, n = 360; lifitegrast, n = 358 (intent-to-treat population). Lifitegrast-treated subjects experienced greater improvement in eye dryness than placebo-treated subjects (treatment effect, 12.61; 95% confidence interval [CI], 8.51-16.70; P < 0.0001). There was no between-group difference in inferior corneal staining (treatment effect, 0.03; 95% CI, -0.10 to 0.17; P = 0.6186). There was nominally significant improvement of secondary symptom end points among lifitegrast-treated subjects: ocular discomfort (nominal P = 0.0005) and eye discomfort (nominal, P < 0.0001). There were no between-group differences on secondary signs: total corneal staining and nasal lissamine staining. More lifitegrast-treated subjects (33.7%) than placebo-treated subjects (16.4%) experienced ocular TEAEs; no ocular TEAEs were serious.
Conclusions: Lifitegrast met the co-primary symptom end point (eye dryness) but not the co-primary sign end point (inferior corneal staining). Secondary end point findings were consistent with this pattern. Most ocular TEAEs were mild to moderate; there were no unexpected TEAEs. Lifitegrast warrants further consideration as a treatment for DED.

Efficacy and Safety of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease: The ONSET-2 Phase 3 Randomized Trial
David Wirta, Patrick Vollmer, James Paauw, Kuei-Hsun Chiu, Eugenia Henry, Kristen Striffler, Jeffrey Nau; ONSET-2 Study Group Collaborators

Purpose: To evaluate the efficacy and safety of OC-01 (varenicline solution) nasal spray for treatment of patients with dry eye disease.
Design: Randomized, multicenter, double-masked, vehicle-controlled, phase 3 study.
Participants: Adults 22 years of age or older with a diagnosis of dry eye disease, artificial tear use, Ocular Surface Disease Index score of 23 or more, and Schirmer test score (STS) of 10 mm or less. Eligibility was not restricted by eye dryness score (EDS).
Methods: Patients (N = 758) were randomized in a 1:1:1 ratio to twice-daily treatment with 50-µl intranasal spray in each nostril of OC-01 0.03 mg (n = 260), OC-01 0.06 mg (n = 246), or vehicle (control; n = 252) for 4 weeks (ClinicalTrials.gov identifier, NCT04036292).
Main outcome measures: The primary efficacy end point was the percentage of patients achieving a 10-mm improvement or more in STS at week 4. Secondary end points included change from baseline to week 4 in STS and EDS in a controlled adverse environment (CAE) chamber and in the clinic. Treatment-emergent adverse events (TEAEs) were assessed.

Results: A statistically significantly greater percentage of patients achieved the primary end point in both OC-01 treatment groups compared with the vehicle group (OC-01 0.03 mg, 47.3%; OC-01 0.06 mg, 49.2%; vehicle, 27.8%; P < 0.0001 for both doses). Change from baseline in STS at week 4 was statistically significantly greater for patients receiving OC-01 than vehicle (P < 0.0001 for both doses). Eye dryness score assessed at week 4 improved with OC-01 treatment compared with vehicle, although the difference was not significant for EDS measured in the CAE chamber and showed (nominal) significance in the clinic. Overall, 86.5% of patients (654/756) reported at least 1 TEAE during the treatment period; most were mild, nonocular (sneezing, cough, throat irritation, and instillation site irritation) and were reported by fewer patients in the vehicle group than in the OC-01 treatment groups (OC-01 0.03 mg, 97.3%; OC-01 0.06 mg, 99.2%; vehicle, 57%).
Conclusions: OC-01 nasal spray was well tolerated and showed a clinically meaningful effect on signs and symptoms of dry eye disease.
Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 26, 2025
Search Strategy:

#	Searches	Results
1	Loteprednol.mp. or Loteprednol Etabonate/	285
2	Lifitegrast.mp.	132
3	varenicline.mp. or Varenicline/	2488
4	perfluorohexyloctane.mp.	109
5	cyclosporine solution.mp.	18
6	1 or 2 or 3 or 4 or 5	3015
7	limit 6 to (english language and humans and yr="2015 -Current")	1130
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	125

Appendix 5: Key Inclusion Criteria

Population	Patients with dry eye disease
Intervention	Prescription drugs for the treatment of dry eye
Comparator	Vehicle or active comparator
Outcomes	Symptomatic improvement of dry eye disease
Setting	Outpatient

Targeted Drugs for Dry Eye Disease

Goal(s):

- Allow for coverage of approved prescription therapies for dry eye disease and vernal keratoconjunctivitis when they are funded in 2027.
- Allow case-by-case review for members covered under the EPSDT program.
- Over-the-counter artificial tears do not require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred prescription drugs for dry eye and vernal keratoconjunctivitis

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a prescription dry eye product or product for vernal keratoconjunctivitis?	**Yes**: Go to Renewal Criteria below	**No:** Go to #4
4. Is the request for a patient with dry eye?	**Yes:** Go to #5	**No:** Go to #10
5. Is the diagnosis funded by OHP?	**Yes:** Go to #8	**No:** Go to #6

Approval Criteria		
6. Does the patient have dry eye resulting in blurred vision or other visual impairment as a result of a chronic eye condition or medical condition (e.g., Sjögren's syndrome, lupus, cataracts, etc.)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; If eligible for EPSDT review go to #7
7. If the member is eligible for EPSDT review, is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical necessity
8. Has the patient tried artificial tears/ocular lubricants for at least 4 weeks without improvement in symptoms?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of artificial tears
9. Is there documentation of baseline dry eye symptoms based on the Ocular Surface Disease Index (OSDI) or visual analog score (VAS)?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; recommend baseline assessment of dry eye symptoms
10. Does the patient have a diagnosis vernal keratoconjunctivitis?	**Yes:** Go to #11	**No:** Pass to RPh. Deny
11. Is the diagnosis funded by OHP?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; If eligible for EPSDT review go to #12.
12. If the member is eligible for EPSDT review, is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
13. Is the medication being prescribed by an optometrist or ophthalmologist?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; recommend referral to optometrist or ophthalmologist.
14. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for a maximum of 12 months.

Renewal Criteria		
1. Is the request for a renewal of a previously approved dry eye disease medication?	**Yes**: Go to #2	**No:** Go to Approval Criteria above
2. Is the request for a patient with dry eye?	**Yes**: Go to #3	**No**: Go to #4
3. Is there documentation of improvement from baseline dry eye symptom scores (e.g., OSDI change of 4.5 units or more or VAS reduction of 30% or more) as assessed by the prescribing provider?	**Yes**: Approve for a maximum of 12 months	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for a patient with vernal keratoconjunctivitis and the provider reports improvement in symptoms (this is a rare disease without validated tools for symptom assessment)?	**Yes**: Approve for a maximum of 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/25 (KS)
Implementation: TBD