Peering into the Dry Eye Pipeline for 2023 and Beyond

Lakshman Mulpuri[1] and Lisa Nijm[2,3]

1. Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA; 2. Warrenville EyeCare & LASIK, Warrenville, IL, USA; 3. Department of Ophthalmology and Visual Sciences, Illinois Eye and Ear Infirmary, Chicago, IL, USA

DOI: https://doi.org/10.17925/USOR.2023.17.2.3

The global prevalence of dry eye disease (DED) ranges between approximately 5% and 50% and engenders a substantial socioeconomic burden. In the past decade, an unprecedented collaboration between industry and the vision sciences has spawned numerous potential therapeutic agents for DED. Many of these options possess novel mechanisms of action, potentially allowing clinicians to better tailor their treatment of patients suffering from DED. This review covers several specific pipeline drugs, such as lotilaner, perfluorohexyloctane, and cyclosporine A, along with broader drug classes such as reactive aldehyde species inhibitors, keratolytics, and mitochondrial reactive oxidative species scavengers. This review will summarize the promise and efficacy of upcoming dry eye disease treatments through the lens of data from USA-based phase II and phase III clinical trials.

Keywords

Clinical trial, dry eye disease, industry, ocular surface disease, pharmaceutical, pipeline

Disclosures: Lisa Nijm is a consultant for Azura, Bausch & Lomb, and Tarsus. Lakshman Mulpuri has no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: 27 March 2023

Accepted: 19 May 2023

Published online: 20 September 2023

Citation: *touchREVIEWS in Ophthalmology.* 2023;17(2):Online ahead of journal publication

Corresponding author: Lisa Nijm, Warrenville EyeCare & LASIK, 2S631 Illinois Rte 59, Warrenville, IL 60555, USA. E: LMNijm@uic.edu

Support: No funding was received in the publication of this article.

Dry eye disease (DED) is a multifactorial condition of the ocular surface and tears. It is frequently encountered in ocular practices, comprising nearly 33% of visits in the USA, and with an estimated global prevalence ranging between 5% and 50%.[1,2] The chronic symptoms and discomfort reported by patients with DED directly impact their quality of life and reduce their ability to complete tasks that require sustained visual attention.[3] Moreover, DED places a significant burden on patients through loss in productivity and high medical costs. When adjusting for the prevalence of DED nationwide, the overall burden of DED on the healthcare system in the USA is estimated to be $3.84 billion.[4] As a result, advances in the management and treatment of patients with DED are significant for reducing DED-associated costs and improving patients' quality of life. There are currently six prescription medications approved by the US Food and Drug Administration (FDA) for the treatment of DED. Three of these drugs, lotilaner (TP-03; Tarsus Pharmaceuticals Inc, Irvine, CA, USA), perfluorohexyloctane ophthalmic solution (PFHO; Miebo™ [formerly NOV03]; Bausch and Lomb, Vaughan, Ontario) and cyclosporine ophthalmic solution (VEVYE™; Novaliq, Heidelberg, Germany) recently received FDA approval in the second quarter 2023.[5–10] These approvals have allowed for the advancement of numerous products with novel mechanisms of action to treat DED and its underlying causes. This article will review some promising dry eye interventions and their current status.

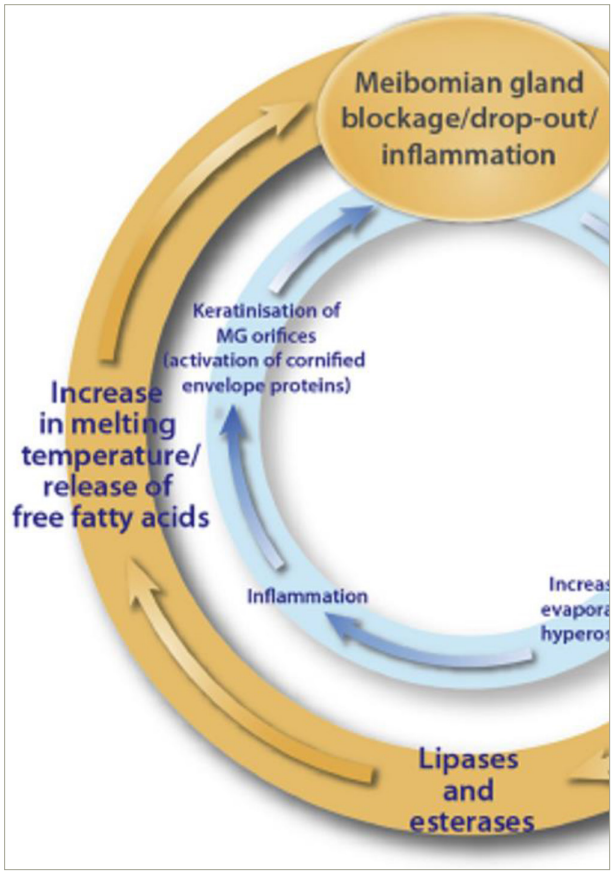
Lotilaner ophthalmic solution

In a recent study, the prevalence of *Demodex* blepharitis in patients with dry eye was estimated to be 58.9%.[11] In patients diagnosed with blepharitis, the prevalence of *Demodex* blepharitis rises to 69.1%.[11] *Demodex folliculorum* infestation is also considered to be a key contributor in the pathogenesis of meibomian gland dysfunction (MGD)-related DED (*Figure 1*).[12] The authors of a 2021 abstract found that ocular *Demodex* infestation may alter meibum composition and progress ocular *Demodex* infections.[13]

A lotilaner ophthalmic solution would be the first treatment for *Demodex* blepharitis approved by the FDA.[14] It is formulated with lotilaner (0.25% ophthalmic solution), a highly lipophilic antiparasitic agent that eradicates *Demodex* mites by selectively inhibiting parasite-specific gamma-aminobutyric acid chloride channels. Its lipophilic nature improves its ability to be uptaken in the oily sebum of the hair follicles where *Demodex* often reside.[15]

Tarsus Pharmaceutical's phase IIb/III pivotal trial, Saturn-2 (ClinicalTrials.gov identifier: NCT04784091), studied 412 patients with *Demodex* blepharitis possessing more than 10 collarettes on the upper lid, at least mild erythema of the upper eyelid margin and an average density of at least 1.5 mites per lash on the upper and lower eyelids combined.[16] One drop of lotilaner ophthalmic solution was administered twice daily in each eye for 43 days. Tarsus reported that lotilaner ophthalmic solution (TP-03) met the study's primary and secondary endpoints while remaining well tolerated. A total of 56% of patients achieved complete collarette cure (grade 0: 0–2 lashes with collarettes per eyelid) compared with 13% of those on placebo by day 43. They also reported that 52% of patients in lotilaner

Figure 1: The interconnectedness of meibomian gland disease and dry eye disease



Reproduced from Baudouin et al.[12] © BMJ, used under the Creative Commons CC-BY-NC 4.0 license.
MG = meibomian gland.

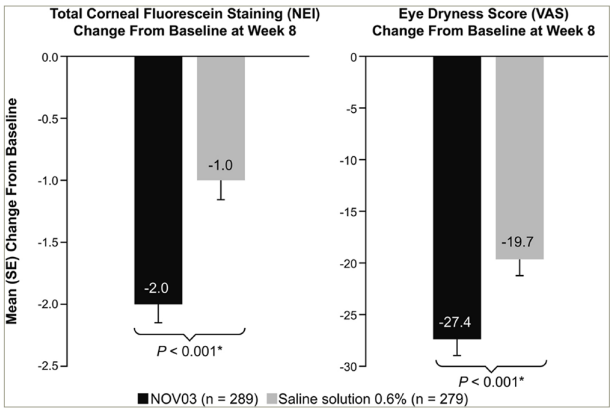
ophthalmic solution group achieved mite eradication (defined as a mite density of zero mites per lash) by day 43, compared with 14% for those in the vehicle group, and about one in three patients accomplished complete lid erythema cure. Additionally, treatment-related ocular adverse events showed that lotilaner ophthalmic solution was well tolerated (*Figure 2*).[17]

Figure 2: Saturn-2 demonstrates lotilaner ophthalmic solution was well tolerated

Treatment related ocular AE rates > 1%		
	TP-03 (n=203)	Vehicle (n=209)
Instillation site pain/burning/stinging	7.9%	6.7%
Visual acuity reduced	0.5%	1.4%
Dry eye	1.5%	0.5%
AE Severity	3 moderate All others mild	1 moderate All others mild

AE = adverse event.
Reproduced from Gaddie et al.[17] © Elsevier, used under Creative Commons CC-BY license.

Figure 3: Primary endpoints of the GOBI phase III trial



Left: change from placebo in total corneal fluorescein staining: statistical significance achieved at day 15, with continued results through day 57 compared with control; mean treatment difference -0.97 on a 15-point scale (p<0.001). Right: change from placebo in dryness score: statistical significance at day 15, with continued results through day 57 compared with control, as rated on a visual analog scale; mean treatment difference -7.6 on a 100-point scale (p<0.001).
NEI = National Eye Institute; SE = standard error; VAS = visual analogue scale.
Reproduced from Tauber et al.[22] © Elsevier, used under Creative Commons CC-BY-NC-ND license.

After the promising results of these two pivotal trials, Tarsus submitted a New Drug Application (NDA) at the end of the third quarter of 2022 and received FDA approval in August 2023.[18]

Perfluorohexyloctane ophthalmic solution

PFHO (100%) is a drug designed specifically for patients with DED secondary to MGD. One drop per eye should be applied four times daily. PFHO has recently attracted attention for its potential to treat DED associated with MGD. An abstract from the 2023 Association for Research in Vision and Ophthalmology meeting found that PFHO layered on top of physiological saline significantly inhibited evaporation rate by 84% while increasing the fluidity of wax esters (components of human meibum)[19] by 64%.[20] As a result, Miebo™, which is composed entirely of PFHO, has a dual mechanism of action; both rapidly covering the cornea and stabilizing the tear film. It may also act by penetrating the meibomian glands and liquefying secretions.

PFHO uses a proprietary water-free, non-steroidal and preservative-free technology named EyeSol® (Novaliq, Heidelberg, Germany).[21] This technology aims to increase the residual time the drug is on the ocular surface while simultaneously enhancing its bioavailability to the intended ocular tissue.

Phase III of the first trial evaluating PFHO, GOBI (ClinicalTrials.gov identifier: NCT04139798), included 597 participants randomized to receive either Miebo four times daily or a hypotonic saline solution four times daily.[22] Results from the study were favourable after 8 weeks, with patients receiving PFHO showing a significantly greater improvement in both endpoints (i.e. eye dryness score and total corneal fluorescein staining [tCFS]) compared with control (*Figure 3*).[22]

After these encouraging results, the company conducted a similar phase III trial, MOJAVE (ClinicalTrials.gov identifier: NCT04567329), with 622 participants randomized to a treatment arm (PFHO) or a placebo arm (saline solution).[23] PFHO met both primary endpoints (i.e. tCFS and eye dryness score), demonstrating similar results to the GOBI trial.[24] The clinical arm of this investigation concluded with a 12-month safety

extension trial, KALAHARI (ClinicalTrials.gov identifier: NCT04140227),[25] after which Bausch and Lomb filed an NDA in September 2022.[26] The product was approved by the FDA in the second quarter of 2023 for the treatment of the signs and symptoms of DED.[27]

Cyclosporine ophthalmic solution

Another property using the EyeSol® technology, cyclosporine ophthalmic solution (VEVYE™; Novaliq, Heidelberg, Germany), is an anti-inflammatory 0.1% cyclosporine A designed to treat DED. In its phase IIb/III trial, ESSENCE (ClinicalTrials.gov identifier: NCT03292809),[28] 328 subjects with DED were randomized to either 0.1% cyclosporine ophthalmic solution or placebo twice daily for 12 weeks and assessed its efficacy, safety and tolerability among participants receiving CyclASol.[29] At week 4, the intervention group was demonstrated to be superior to placebo for tCFS, a difference that was already achieved by week 2. Additionally, the drop was well tolerated, with minimal side effects.

The second iteration of this study, ESSENCE-2 (ClinicalTrials.gov identifier: NCT04523129),[30] included a larger cohort of participants with DED (N=834) and, again, cyclosporine ophthalmic solution demonstrated a clinically significant improvement in tCFS by week 4.[31] A total of 71.6% of patients receiving cyclosporine ophthalmic solution improved by ≥3 grades in tCFS. Participants also enjoyed statistically significant improvements in a number of other dry-eye-related metrics such as dryness, blurred vision, difficulty looking at screens and difficulty driving at night. The clinical development programme for cyclosporine ophthalmic solution will conclude with an on-going multicentre, open-label, single-arm, 12-month safety extension trial (ESSENCE-2 OLE [also known as CYS-005]; ClinicalTrials.gov identifier: NCT01938248).[32] In the second quarter of 2023, Novaliq announced FDA approval of cyclosporine ophthalmic solution for the treatment of the signs and symptoms of DED.[33]

Reproxalap

Reproxalap (ADX-102; Aldeyra Therapeutics Inc, Lexington, MA, USA) is a small-molecule reactive aldehyde species (RASP) inhibitor that was investigated in the phase II/III TRANQUILITY trial (ClinicalTrials.gov identifier: NCT04674358), which completed in the second quarter of 2022.[34] RASP have been implicated in the pathogenesis of dry eye, and this innovative drug binds with them to free aldehydes, simultaneously reducing inflammation and overall RASP levels.[35]

The phase III trial, TRANQUILITY 2 (ClinicalTrials.gov identifier: NCT05062330),[36] investigated the impact of reproxalap on Schirmer's tests in a cohort of 361 participants with DED. The trial found that 0.25% reproxalap ophthalmic solution was statistically superior when compared with placebo for two specified primary endpoints: a change from baseline on Schirmer's test and ≥10 mm Schirmer's test responder proportions after a single day of dosing.[37]

Interestingly, reproxalap was also selected for a separate phase III trial, ALLEVIATE (ClinicalTrials.gov identifier: NCT03494504), investigating allergic conjunctivitis.[38] This is particularly impactful given the potential overlap between ocular allergy and DED and their concomitant nature. Long-standing alterations in the tear film, corneal innervation and the epithelial barrier found in ocular allergies may open the door to DED. Furthermore, antihistamine medications may decrease tear production and lead to signs of dry eye.[39] Aldeyra reported positive results from their ALLEVIATE trial, demonstrating clinically significant reductions in ocular itch score compared with placebo.[40]

With their successful combined phase II and phase III clinical results, Aldeyra submitted an NDA for ocular topical reproxalap to the FDA in the final quarter of 2022,[41] with a PDUFA target action date of 23 November 2023.[42]

Selenium sulphide ointment

DED is traditionally attributed to either impaired lacrimal production (or aqueous-deficient dry eye) or MGD (or evaporative dry eye); however, there is a significant overlap between the two aetiologies. Over 86% of patients suffering from DED have elements of MGD, and this has become a substantial area of research.[43] Current treatments of MGD include lid hygiene measures (warm compresses and mechanical massaging of the eyelids), artificial tears and lubricating products, and supplementation of omega-3 acids.[44]

However, in 2010, Blackie et al. described abnormal keratinization and aggregation within the meibomian gland duct as a potential primary mechanism in the pathogenesis of MGD.[45] This process has also been termed hyperkeratinization.[46] As a result, recent investigations have demonstrated that the modification of keratin pathways may offer novel mechanistic treatments, spawning the development of keratolytic medications.[47]

Selenium sulphide ointment (AZR-MD-001; Azura Ophthalmics Ltd, Tel Aviv, Israel) is the first brand of keratolytic agents for treating lid margin diseases and associated conditions. Keratolytics have been proposed as potent agents to break disulfide bonds that bind keratin into aggregates and disrupt meibomian gland function.[47] These agents have enjoyed moderate success in other dermatological conditions involving keratinization, such as comedonal acne and seborrheic dermatitis.[47]

A recent phase IIb study evaluated the safety and efficacy of selenium sulphide ointment in 245 patients with MGD. Each patient was administered with the ointment twice weekly to the lower eyelid at bedtime. Patients receiving 0.5% concentration of the ointment demonstrated statistically significant improvements in Meibomian Glands Yielding Liquid Secretion and Ocular Surface Disease Index© scores by the end of the 3-month trial period.[48] Patients experienced an average increase of 1.8 more open glands secreting meibum from baseline (p=0.0004). With regards to Ocular Surface Disease Index, patients reported an average improvement of 3.5 from baseline (p=0.0438) and, at the end of month 3, 46.9% of participants became asymptomatic.

These results are a promising step in advancing multimodal treatments for patients suffering from DED due to MGD, and Azura expects to initiate a second clinical trial in 2023 to continue evaluating selenium sulphide ointment.

SkQ1

SkQ1 (Visomitin®; Mitotech Pharma, Luxembourg, Luxembourg) is an ophthalmic formulation of the antioxidant SkQ1, a small molecule cardiolipin peroxidation inhibitor currently being investigated to treat moderate-to-severe dry eye. The mechanism of action includes combating inflammatory breakdown products and alleviating mitochondrial metabolism. It may also impact corneal epithelial repair and healing.

One of the first phase IIb/III trials evaluating SkQ1 in 450 patients with DED, VISTA-1 (ClinicalTrials.gov identifier: NCT03764735), found a significant reduction in ocular discomfort with excellent tolerability and minimal side effects compared with placebo.[49] VISTA-2 enrolled

a larger cohort (n=610) and demonstrated similar results to VISTA-1.[49] Although the co-primary endpoints (i.e. change from baseline in central corneal fluorescein staining and in grittiness) were not met, both trials demonstrated significant improvements in the key pre-determined secondary endpoint, that is, central corneal fluorescein staining relative to vehicle in a large sub-population defined by Schirmer's score by week 4.

Bolstered by these promising trial results, SkQ1's unique mechanism of action targeting oxidative stress within mitochondria will provide significant momentum, leading into the company's next trial, VISTA-3.

Conclusion

In recent years, there have been a number of approvals for new treatment options. This pipeline has continued to grow rapidly as knowledge of DED has expanded, spurring numerous novel mechanistic innovations to treat the various manifestations of DED. In addition to increased patient awareness, an expanded set of DED tools will uniquely position ophthalmic providers to improve the existing standard of care while minimizing disease burden for patients. ❑

1. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol*. 2017;182:90–8. DOI: 10.1016/j.ajo.2017.06.033.
2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334–65. DOI: 10.1016/j.jtos.2017.05.003.
3. Uchino M, Schaumberg DA. Dry eye disease: Impact on quality of life and vision. *Curr Ophthalmol Rep*. 2013;1:51–7. DOI: 10.1007/s40135-013-0009-1.
4. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: A decision tree analysis. *Cornea*. 2011;30:379–87. DOI: 10.1097/ICO.0b013e3181f7f363.
5. Oyster pointOyster point pharma announces FDA approval of TYRVAYA™ (varenicline solution) nasal spray for the treatment of the signs and symptoms of dry eye disease . 2021. Available at: https://investors.oysterpointrx.com/news-releases/news-release-details/oyster-point-pharma-announces-fda-approval-tyrvayatm-varenicline (Date last accessed: 7 June 2023).
6. Healio.FDA approves Eysuvis for short-term dry eye disease treatment. 2020. Available at: www.healio.com/news/ophthalmology/20201027/fda-approves-eysuvis-for-shortterm-dry-eye-disease-treatment (Date last accessed: 7 June 2023).
7. U.S. Food and Administration.FDA approves first generic of Restasis. 2022. Available at: www.fda.gov/news-events/press-announcements/fda-approves-first-generic-restasis (Date last accessed: 7 June 2023).
8. U.S. Food and Drug Administration.FDA approves new medication for dry eye disease. 2016. Available at: www.fda.gov/news-events/press-announcements/fda-approves-new-medication-dry-eye-disease (Date last accessed: 7 June 2023).
9. businesswire. Bausch + Lomb and Novaliq announce FDA approval of MIEBO™ (perfluorohexyloctane ophthalmic solution) for the treatment of the signs and symptoms of dry eye disease . 2023. Available at: www.businesswire.com/news/home/20230518005700/en/Bausch-Lomb-and-Novaliq-Announce-FDA-Approval-of-MIEBO-Perfluorohexyloctane-Ophthalmic-Solution-for-the-Treatment-of-the-Signs-and-Symptoms-of-Dry-Eye-Disease (Date last accessed: 7 July 2023).
10. businesswire. Novaliq ANNOUNCES FDA approval of VEVYE™ (cyclosporine ophthalmic solution) 0.1% for the treatment of the signs and symptoms of dry eye disease . 2023. Available at: www.businesswire.com/news/home/20230608005090/en/Novaliq-Announces-FDA-Approval-of-VEVYE-Cyclosporine-Ophthalmic-Solution-0.1-for-the-Treatment-of-the-Signs-and-Symptoms-of-Dry-Eye-Disease (Date last accessed: 7 July 2023).
11. Trattler W, Karpecki P, Rapoport Y, et al. The prevalence of *Demodex* blepharitis in US eye care clinic patients as determined by collarettes: A pathognomonic sign. *Clin Ophthalmol*. 2022;16:1153–64. DOI: 10.2147/OPTH.S354692.
12. Baudouin C, Messmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of Meibomian gland dysfunction. *Br J Ophthalmol*. 2016;100:300–6. DOI: 10.1136/bjophthalmol-2015-307415.
13. Gao H, Chen H, Xie H-T, et al. Changes in meibum lipid composition with ocular Demodex infestation. *Transl Vis Sci Technol*. 2021;10:6. DOI: 10.1167/tvst.10.14.6.
14. Hutton D, Reports OS. Tarsus submits NDA to the FDA for TP-03 for treatment of Demodex blepharitis. 2022. Available at: www.ophthalmologytimes.com/view/tarsus-submits-nda-to-the-fda-for-tp-03-for-treatment-of-demodex-blepharitis (Date last accessed: 7 June 2023).
15. Fromstein SR, Harthan JS, Patel J, Opitz DL. Demodex blepharitis: Clinical perspectives. *Clin Optom (Auckl)*. 2018;10:57–63. DOI: 10.2147/OPTO.S142708.
16. Tarsus Pharmaceuticals. Tarsus ANNOUNCES positive Topline data from Saturn-2 phase 3, the second pivotal trial of TP-03 for the treatment of Demodex Blepharitis, and expects to file a new drug application this year. 2022. Available at: https://ir.tarsusrx.com/news-releases/news-release-details/tarsus-announces-positive-topline-data-saturn-2-phase-3-second (Date last accessed: 16 March 2023).
17. Gaddie IB, Donnenfeld ED, Karpecki P, et al. Lotilaner ophthalmic solution, 0.25% for Demodex Blepharitis: randomized, vehicle-controlled, multicenter, phase 3 trial (Saturn-2). *Ophthalmology*. 2023;S0161-6420(23)00392-5. DOI: 10.1016/j.ophtha.2023.05.030.
18. Tarsus PharmaceuticalsTarsus reports third quarter 2022 financial results and recent business achievements. 2022. Available at: https://ir.tarsusrx.com/news-releases/news-release-details/tarsus-reports-third-quarter-2022-financial-results-and-recent (Date last accessed: 7 June 2023).
19. Chen J, Green KB, Nichols KK. Compositional analysis of wax esters in human meibomian gland secretions by direct infusion electrospray Ionization mass spectrometry. *Lipids*. 2016;51:1269–87. DOI: 10.1007/s11745-016-4183-4.
20. Borchman D, Vittitow J, Ewurum A, Veligandla S. Spectroscopic study of perfluorohexyloctane–human meibum interactions. *Invest Ophthalmol Vis Sci*. 2022;63:1525–A0250.
21. Novaliq.Eyesol® Technology. Available at: www.novaliq.com/technology/#substances-used (Date last accessed: 7 June 2023).
22. Tauber J, Berdy GJ, Wirta DL, et al. NOV03 for dry eye disease associated with meibomian gland dysfunction: Results of the randomized phase 3 GOBI study. *Ophthalmology*. 2023;130:516–24. DOI: 10.1016/j.ophtha.2022.12.021.
23. ClinicalTrials.gov. Effect of NOV03 on signs and symptoms of dry eye disease associated with meibomian gland dysfunction (Mojave study). ClinicalTrials.gov: NCT04567329. Available at: https://clinicaltrials.gov/ct2/show/study/NCT04567329 (Date last accessed: 11 May 2022).
24. Sheppard JD, Kurata F, Epitropoulos AT, et al. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: The randomized phase 3 MOJAVE study. *Am J Ophthalmol*. 2023;252:265–74. DOI: 10.1016/j.ajo.2023.03.008.
25. ClinicalTrials.gov. Long-term safety and tolerability of NOV03 (perfluorohexyloctane) in subjects who completed trial NVU-003 (Kalahari study). ClinicalTrials.gov: NCT04140227. Available at: https://clinicaltrials.gov/ct2/show/NCT04140227 (Date last accessed: 19 January 2022).
26. Drugs.comBausch + Lomb and Novaliq announce submission of new drug application for investigational treatment Nov03 (Perfluorohexyloctane). 2022. Available at: www.drugs.com/nda/nov03_220707.html (Date last accessed: 7 June 2023).
27. Drugs.comDrugs.Com. Bausch + Lomb and Novaliq announce U.S FDA filing acceptance for investigational treatment Nov03 (Perfluorohexyloctane). 2023. Available at: www.drugs.com/nda/nov03_220906.html (Date last accessed: 7 June 2023).
28. ClinicalTrials.gov. Cyclasol for the treatment of signs and symptoms of dry eye disease (DED). ClinicalTrials.gov Identifier: NCT03292809. Available at: https://clinicaltrials.gov/ct2/show/NCT03292809 (Date last accessed: 22 December 2022).
29. Sheppard JD, Wirta DL, McLaurin E, et al. A water-free 0.1% cyclosporine A solution for treatment of dry eye disease: Results of the randomized phase 2b/3 ESSENCE study. *Cornea*. 2021;40:1290–7. DOI: 10.1097/ICO.0000000000002633.
30. ClinicalTrials.gov. ESSENCE 2: CyclASol for the treatment of signs and symptoms of dry eye disease (DED). ClinicalTrials.gov: NCT04523129. Available at: https://clinicaltrials.gov/ct2/show/NCT04523129 (Date last accessed: 10 March 2023).
31. Akpek EK, Wirta DL, Downing JE, et al. 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. *JAMA Ophthalmol*. 2023;141:459–66. DOI: 10.1001/jamaophthalmol.2023.0709.
32. ClinicalTrials.govApixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA). ClinicalTrials.gov Identifier: NCT01938248. Available at: https://clinicaltrials.gov/ct2/show/NCT01938248 (Date last accessed: 7 June 2023).
33. Novaliq. Novaliq announces FDA acceptance of the new drug application for Cyclasol® for the treatment of dry eye disease. 2023. Available at: www.novaliq.com/press-releases/2022/10/24/novaliq-announces-fda-acceptance-of-the-new-drug-application-for-cyclasol-for-the-treatment-of-dry-eye-disease/ (Date last accessed: 7 June 2023).
34. ClinicalTrials.govThe TRANQUILITY trial: Clinical trial to assess the efficacy and safety in subjects with dry eye disease. ClinicalTrials.gov Identifier NCT04674358. Available at: https://clinicaltrials.gov/ct2/show/NCT04674358 (Date last accessed: 7 June 2023).
35. Clark D, Sheppard J, Brady TC. A randomized double-masked phase 2a trial to evaluate activity and safety of topical ocular reproxalap, a novel RASP inhibitor, in dry eye disease. *J Ocul Pharmacol Ther*. 2021;37:193–9. DOI: 10.1089/jop.2020.0087.
36. ClinicalTrials.gov. The TRANQUILITY 2 trial: A phase 3 clinical trial to assess the efficacy and safety in subjects with dry eye disease. ClinicalTrials.gov Identifier: NCT05062330. Available at: https://clinicaltrials.gov/ct2/show/study/NCT05062330 (Date last accessed: 17 February 2023).
37. Aldeyra. Aldeyra Therapeutics achieves primary endpoint in phase 3 TRANQUILITY-2 trial in dry eye disease and intends to submit new drug application for symptoms and three sign endpoints of dry eye disease. 2022. Available at: https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-achieves-primary-endpoint-phase-3 (Date last accessed: 7 June 2023).
38. ClinicalTrials.gov. ALLEVIATE trial - A phase 3 trial in subjects with allergic conjunctivitis. ClinicalTrials.gov Identifier: NCT03494504. Available at: https://clinicaltrials.gov/ct2/show/NCT03494504 (Date last accessed: 6 November 2019).
39. Foutch BK, Sandberg KA, Bennett ES, Naeger LL. Effects of oral antihistamines on tear volume, tear stability, and intraocular pressure. *Vision (Basel)*. 2020;4:32. DOI: 10.3390/vision4020032.
40. Aldeyra. Aldeyra Therapeutics announces positive top-line results from the phase 3 ALLEVIATE trial in patients with allergic conjunctivitis. 2019. Available at: https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-announces-positive-top-line-results-phase-3 (Date last accessed: 7 June 2023).
41. Aldeyra. Aldeyra Therapeutics announces FDA acceptance of new drug application for reproxalap for the treatment of dry eye disease. 2023. Available at: https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-announces-fda-acceptance-new-drug (Date last accessed: 7 June 2023).
42. Aldeyra. Aldeyra Therapeutics submits new drug application to the U.S. Food and Drug Administration for reproxalap for the treatment of signs and symptoms of dry eye disease. 2022. Available at: https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-submits-new-drug-application-us-food-and (Date last accessed: 20 June 2023).
43. Rabensteiner DF, Aminfar H, Boldin I, et al. The prevalence of meibomian gland dysfunction, tear film and ocular surface parameters in an Austrian dry eye clinic population. *Acta Ophthalmol*. 2018;96:e707–11. DOI: 10.1111/aos.13732.
44. Chuckpaiwong V, Nonpassopon M, Lekhanont K, et al. Compliance with lid hygiene in patients with Meibomian gland dysfunction. *Clin Ophthalmol*. 2022;16:1173–82. DOI: 10.2147/OPTH.S360377.
45. Blackie CA, Korb DR, Knop E, et al. Nonobvious obstructive meibomian gland dysfunction. *Cornea*. 2010;29:1333–45. DOI: 10.1097/ICO.0b013e3181d4f366.
46. Du Y-L, Peng X, Liu Y, et al. Ductal hyperkeratinization and acinar renewal abnormality: New concepts on pathogenesis of meibomian gland dysfunction. *Curr Issues Mol Biol*. 2023;45:1889–901. DOI: 10.3390/cimb45030122.
47. Gupta PK, Periman LM, Lain E, et al. Meibomian gland dysfunction: A dermatological perspective on pathogenesis and treatment outlook. *Clin Ophthalmol*. 2021;15:4399–404. DOI: 10.2147/OPTH.S327407.
48. AzuraOphthalmics. Azura Ophthalmics presents positive results from phase 2b clinical trial of AZR-MD-001 in meibomian gland dysfunction at Ophthalmology Innovation Summit XII [Internet]. Available at: https://azuraophthalmics.com/press-releases/azura-ophthalmics-presents-positive-results-from-phase-2b-clinical-trial-of-azr-md-001-in-meibomian-gland-dysfunction-at-ophthalmology-innovation-summit-xii/ (Date last accessed: 16 March 2023).
49. Ousler GW, Watson M, Sheppard JD, et al. Safety and efficacy of ophthalmic mitochondrial reactive oxygen species scavenger Visomitin for the treatment of dry eye disease: Findings of VISTA-1 and VISTA-2 studies. *Invest Ophthalmol Vis Sci*. 2022;63:1555–A0280.