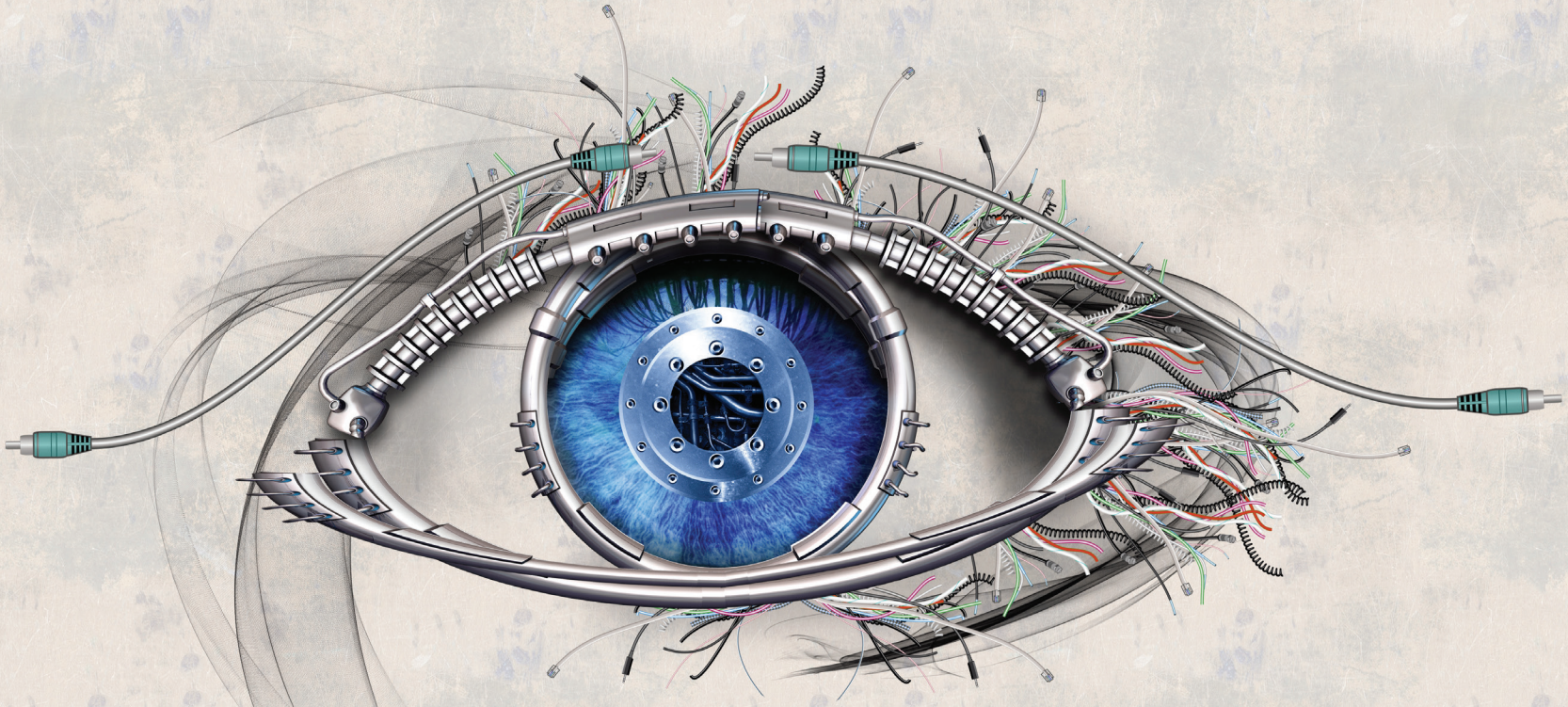

DRY EYE BREAKTHROUGHS IN THE MAKING

From meibomian gland dysfunction to neurotrophic keratopathy, investigational therapies are tackling key challenges in dry eye management.

BY MICHELE CORRY, EDITOR-IN-CHIEF, WITH ERIC D. DONNENFELD, MD, AND DAVID J. CALKINS, PHD

Dry eye disease (DED) continues to frustrate surgeons and patients alike with its multifactorial nature and resistance to one-size-fits-all solutions. Although current therapies offer varying degrees of relief, a growing pipeline of investigational treatments is targeting the root causes of ocular surface disease. From addressing meibomian gland dysfunction (MGD) to advancing care for neurotrophic keratopathy (NK), these therapies could reshape the management of complex cases.

With contributions from Eric D. Donnenfeld, MD, and David J. Calkins, PhD, this article explores a range of promising investigational treatments—including a keratolytic for MGD, a reactive aldehyde species modulator, a melanocortin receptor agonist, and more. An examination of clinical trial data, mechanisms of action, and potential limitations provides a comprehensive overview of the innovative approaches that may shape the future of DED care.

A NOVEL OPHTHALMIC KERATOLYTIC FOR MGD

AZR-MD-001 (0.5% ophthalmic ointment, Azura Ophthalmics) uses selenium sulfide to treat the underlying pathophysiology of MGD. The compound has a multimodal mechanism of action, including softening keratin blockages within the meibomian glands, reducing abnormal keratin production to prevent future obstructions, and enhancing the quality and quantity of meibum secretion.[1,2]

PHASE 2B CLINICAL TRIAL RESULTS

In a multicenter, double-masked, vehicle-controlled trial, 245 patients with MGD were treated with AZR-MD-001 twice weekly for 3 months.[1] The study met its coprimary endpoints, demonstrating

significant improvements in both signs and symptoms:

- An average increase of 1.8 open glands from baseline (P = .0004) and
- An average improvement of 3.5 points from baseline (P = .0438).

Secondary outcomes included improvements in meibum quality, tear stability, and patient-reported outcomes such as the Standard Patient Evaluation of Eye Dryness and visual analogue scale. A total of 46.9% of patients achieved asymptomatic Ocular Surface Disease Index scores, and 68.7% saw their meibum quality return to normal levels.

SAFETY AND TOLERABILITY

AZR-MD-001 was well tolerated, with most adverse events reported as mild and transient. Treatment-related discontinuations occurred in only 2.4% of patients. No serious treatment-related adverse events were observed, supporting the favorable safety profile of the product.

PHASE 3 AND BEYOND

Building on these phase 2b findings, the ASTRO study represents a pivotal phase 3 trial assessing AZR-MD-001 in 500 patients.[2] This study aims to confirm its safety, efficacy, and tolerability over a 12-month period.

CLINICAL IMPLICATIONS

By directly targeting the glandular dysfunction underlying MGD, AZR-MD-001 has the potential to reshape current management approaches. Its ability to enhance gland function and provide long-lasting symptom relief may benefit the many patients who experience the downstream consequences of MGD.

1. Azura Ophthalmics. Azura Ophthalmics announces positive results from phase 2b clinical trial of AZR-MD-001 in meibomian gland dysfunction. November 17, 2022. Accessed December 20, 2024. azuraophthalmics.com/press-releases/azura-ophthalmics-announces-positive-results-from-phase-2b-clinical-trial-of-azr-md-001-in-meibomian-gland-dysfunction
2. Azura Ophthalmics. Azura Ophthalmics announces enrollment of first patient in phase 3 clinical trial for AZR-MD-001 in patients with meibomian gland dysfunction. June 4, 2024. Accessed December 20, 2024. azuraophthalmics.com/press-releases/azura-ophthalmics-announces-enrollment-of-first-patient-in-phase-3-clinical-trial-for-azr-md-001-in-patients-with-meibomian-gland-dysfunction

A NOVEL REACTIVE ALDEHYDE SPECIES MODULATOR

Reproxalap (0.25% ophthalmic solution, Aldeyra Therapeutics) is a first-in-class small-molecule modulator of reactive aldehyde species, which are elevated in inflammatory diseases. By inhibiting reactive aldehyde species, reproxalap reduces inflammation associated with DED. This mechanism has been validated through consistent, statistically significant improvements in clinical trials, positioning reproxalap as a potential game-changer in DED management.[1,2]

PHASE 3 CLINICAL TRIAL RESULTS

The efficacy of reproxalap was evaluated in a randomized, double-masked, vehicle-controlled dry eye chamber trial.[2] The trial enrolled 132 patients (66 receiving reproxalap and 66 receiving vehicle) and assessed ocular discomfort as the primary endpoint. Reproxalap demonstrated statistically significant superiority over the vehicle in reducing ocular discomfort (P = .004) between 80 and 100 minutes of chamber exposure, marking the first phase 3 DED trial to achieve this symptom-based endpoint. The study was designed to fulfill the US FDA's requirements for New Drug Application resubmission following a Complete Response Letter.

SAFETY AND TOLERABILITY

Reproxalap was well tolerated, with no serious adverse events reported. The most commonly observed adverse effect was mild and transient discomfort at the instillation site. These findings are consistent with earlier studies of reproxalap, which has now been evaluated in more than 2,500 patients with no significant safety concerns.[2]

CLINICAL IMPLICATIONS

Reproxalap has demonstrated efficacy for both acute and chronic DED symptoms, including ocular redness and discomfort. The drug's novel mechanism of action and rapid onset of effect could distinguish it from existing therapies, providing relief for patients who experience insufficient benefit from current options.

1. Aldeyra Therapeutics, Inc. Reproxalap: our novel small molecule drug candidate for dry eye. Aldeyra Therapeutics, Inc. 2024. Accessed December 20, 2024. https://www.aldeyra.com/pipeline-disease-areas/ocular-diseases/dry-eye-disease
2. Aldeyra Therapeutics, Inc. Aldeyra Therapeutics achieves primary endpoint in phase 3 dry eye disease clinical trial of reproxalap. Business Wire. August 8, 2024. Accessed December 20, 2024. https://www.businesswire.com/news/home/20240808408806/en/Aldeyra-Therapeutics-Achieves-Primary-Endpoint-in-Phase-3-Dry-Eye-Disease-Clinical-Trial-of-Reproxalap

A MELANOCORTIN RECEPTOR AGONIST

PL9643 (Palatin) takes an innovative approach to managing DED by leveraging the antiinflammatory and immunomodulatory properties of the melanocortin receptor system.[1] As a melanocortin receptor agonist, PL9643 is designed to address both the symptoms and underlying pathology of DED. By activating natural pathways to reduce inflammation and enhance tissue healing, PL9643 differs from conventional therapies that primarily target tear production or isolated inflammation.

PHASE 3 RESULTS

The phase 3 MELODY-1 trial demonstrated robust clinical efficacy across multiple endpoints.

Symptom relief. The coprimary endpoint of pain achieved statistical significance at 12 weeks (P < .025), with sustained improvements observed over the treatment period. Seven of 11 secondary symptom endpoints also reached significance (P < .05).

Rapid onset of action. As early as 2 weeks after treatment initiation, improvements were noted in both

symptom and sign endpoints, including all four fluorescein staining measures ($P < .05$), indicating enhanced corneal health.

Safety profile. PL9643 demonstrated favorable tolerability compared with vehicle, with fewer adverse events and discontinuations. Ocular adverse events occurred in 5.6% of PL9643-treated patients versus 6.3% in the vehicle group.[1]

CLINICAL IMPLICATIONS

The combination of early and sustained efficacy, coupled with an excellent safety profile, suggests that PL9643 could transform DED management by benefiting both newly diagnosed patients and those with refractory disease. This pharmacologic alternative would align with patient preferences for noninvasive, rapid, and durable relief.

1. Palatin Technologies, Inc. Palatin announces phase 3 PL9643 MELODY-1 dry eye disease (DED) clinical data results presented at American Society of Cataract and Refractive Surgery (ASCRS) 2024. April 8, 2024. Accessed December 19, 2024. https://palatin.com/press_releases/palatin-announces-phase-3-pl9643-melody-1-dry-eye-disease-ded-clinical-data-results-presented-at-american-society-of-cataract-and-refractive-surgery-ascrs-2024

THYMOSIN BETA 4

The product 0.1% RGN-259 Ophthalmic Solution (ReGenTree) contains thymosin beta 4, a regenerative protein naturally present in tears that plays a pivotal role in promoting corneal healing, reducing inflammation, and improving cellular survival.[1] Thymosin beta 4 enhances epithelial cell migration, stem cell recruitment, and laminin-332 production, potentially addressing the unique challenges presented by NK.[1] NK is a rare and severe ocular disease that can lead to persistent epithelial defects and vision loss.

CLINICAL TRIAL OUTCOMES

The SEER-1 study assessed the safety and efficacy of RGN-259 in patients with stage 2 or 3 NK.[1]

Enhanced healing. By day 29, 60% of eyes treated with RGN-259 achieved complete healing compared to 12.5% in the placebo group. Healing persisted for 2 weeks after therapy ceased ($P = .0359$) with no recurrent defects observed in the RGN-259 group.

Improved clinical outcomes. Patients experienced significant improvements in Mackie classification, with 80% showing lower disease stages or complete healing by day 29 compared to 25% in the placebo group.

Rapid onset of relief. Patients treated with RGN-259 reported substantial reductions in ocular discomfort, dryness, and foreign body sensation by day 15, outcomes not observed in the placebo group.

Safety. RGN-259 was well tolerated, with no significant drug-related adverse events.

ADVANTAGES

Ease of use. RGN-259 is administered five times daily and can be stored at room temperature.

Cost-effectiveness. The formulation's storage requirements and cost structure enhance accessibility and support patient compliance.

Rapid action. In the SEER-1 study, RGN-259 efficiently promoted epithelial healing, potentially reducing the burden of treatment and helping to address long-term complications such as scarring.

NEXT STEPS AND OUTLOOK

The SEER-1 study highlights the therapeutic potential of RGN-259, but the sample size was small. Larger studies are required to confirm efficacy and long-term benefits. Further exploration of the drug's role in nerve regeneration and scar prevention may broaden its clinical applications.

1. Sosne G, Kleinman HK, Springs C, Gross RH, Sung J, Kang S. 0.1% RGN-259 (Thymosin ß4) ophthalmic solution promotes healing and improves comfort in neurotrophic keratopathy patients in a randomized, placebo-controlled, double-masked phase III clinical trial. *Int J Mol Sci*. 2022;24(1):554.

TRPM8: A NOVEL TARGET IN DED

BY ERIC D. DONNENFELD, MD

Many current therapies, including corticosteroids, cyclosporine, and lifitegrast (Xiidra, Bausch + Lomb), target T-cell modulation. Other newer treatments, such as perfluorohexyloctane ophthalmic solution (a tear stabilization agent; Miebo, Bausch + Lomb) and varenicline solution nasal spray 0.03 mg (a secretagogue; Tyrvaya, Visiometrics), have expanded the therapeutic landscape. However, there is a pressing demand for novel treatments employing innovative mechanisms of action.

Transient receptor potential melastatin 8 (TRPM8), also known as the *cold and menthol receptor 1*, is a cation channel involved in detecting innocuous cold temperatures.[1] TRPM8 was first identified in 2002 by the Julius and Patapoutian laboratories, whose work earned the Nobel Prize in 2021.[2] Their research demonstrated that TRPM8 activation is essential for the sensation of cold, with TRPM8-deficient mice exhibiting deficits in perceiving innocuous cold stimuli.

TRPM8 is expressed on sensory nerve endings in the trigeminal ganglion that innervates the corneas and eyelids. Tear evaporation on the ocular surface reduces temperature, activating TRPM8. This triggers the trigeminal nerve to stimulate the lacrimal and meibomian glands; causes goblet cells to produce aqueous, lipids,

ANOTHER TRPM8 AGONIST

BY MICHELE CORRY, EDITOR-IN-CHIEF

IVW-1001 (iView Therapeutics) is a TRPM8 agonist designed to address the signs and symptoms of dry eye disease.[1] Delivered via an ophthalmic eyelid wipe, IVW-1001 offers a novel, patient-friendly approach that could improve accessibility and compliance compared to traditional eye drop formulations.

PHASE 1/2 TRIAL

Patient recruitment has been completed for a phase 1/2 clinical trial of IVW-1001. The trial will evaluate the product's safety, tolerability, and efficacy for the treatment of DED.[1]

ADVANTAGES AND DIFFERENTIATION

Ophthalmic eyelid wipes eliminate the need for precise drop instillation, which can be challenging for some patients. IVW-1001's unique mechanism may provide patients with early symptomatic relief, addressing a critical unmet need.

1. IVIEW Therapeutics Inc. completes patient recruitment for phase 1/2 trial of IVW-1001 ophthalmic eyelid wipe in dry eye disease patients. IVIEW Therapeutics Inc. September 17, 2024. Accessed December 19, 2024. https://www.prnewswire.com/news-releases/iview-therapeutics-inc-completes-patient-recruitment-for-phase-12-trial-of-ivw-1001-ophthalmic-eyelid-wipe-in-dry-eye-disease-patients-302250696.html

and mucins; and thereby supports tear film integrity and ocular surface health.

A FIRST-IN-CLASS TRPM8 AGONIST

AR-15512 (Alcon) is a topical, selective, and potent TRPM8 agonist and a first-in-class approach to DED treatment. By modulating trigeminal nerve activity, AR-15512 stimulates basal tear production, addressing a key physiologic deficit in DED. Persistent stimulation of tear production by AR-15512 could significantly improve ocular surface health.

Clinical Trial Insights

AR-15512 was evaluated in two pivotal US FDA clinical trials, COMET-2 and COMET-3, which collectively enrolled more than 930 patients with DED.[2] Participants were randomly assigned 1:1 to receive either AR-15512 or a vehicle control. The trials achieved their primary endpoint: a statistically significant proportion of patients showed at least a 10-mm increase in unanesthetized Schirmer scores by day 14 ($P < .0001$).

Secondary endpoint analyses highlighted the rapid onset and sustained efficacy of AR-15512, with improvements in tear production observed as early as day 1 and persisting through day 90. These findings align with the proposed mechanism of action of TRPM8 activation.

Safety and Tolerability

AR-15512 was well tolerated across both trials, with no serious ocular adverse events reported. This favorable safety profile supports the drug's potential as a transformative treatment for DED.

CLINICAL POTENTIAL

AR-15512 is currently under US FDA review. The drug's approval would provide clinicians with a groundbreaking addition to the DED therapeutic arsenal that offers a novel mechanism of action along with rapid and sustained benefits. ■

1. Powell W. AR-15512, a novel topical drug candidate for dry eye disease. *touchREVIEWS in Ophthalmology*. 2024;19(1):1-2. https://touchophthalmology.com/corneal-and-external-disorders/journal-articles/ar-15512-a-novel-topical-drug-candidate-for-dry-eye-disease/
2. The Nobel Assembly at Karolinska Institutet. The Nobel Prize in Physiology or Medicine 2021 [press release]. NobelPrize.org. October 4, 2021. Accessed December 19, 2024. https://www.nobelprize.org/prizes/medicine/2021/press-release/

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COLLAGEN MIMETIC PEPTIDES FOR OCULAR SURFACE DISEASE

BY DAVID J. CALKINS, PHD

An ongoing phase 3 clinical trial (NCT06178679) is evaluating ST-100 (vezocolmitide, Stuart Therapeutics) in 320 patients with DED. The drug candidate is part of the company's PolyCol platform, a suite of collagen mimetic peptides designed for ocular disorders. Unlike peptide fragments derived from chemically digested collagen, these mimetic peptides are synthetic constructs that precisely repair damaged endogenous collagen degraded by protease activity during inflammation or injury.[1]

By intercalating into damaged collagen, mimetic peptides restore the natural triple-helical structure essential for collagen's stability and extracellular matrix (ECM) functions. This dual activity of structural repair and restoration of healthy collagen signaling helps reduce inflammation, promote cell growth, and support tissue integrity. Since 90% of the cornea comprises collagen, damage caused by DED represents a significant area of therapeutic opportunity. ST-100 disrupts the cycle of inflammation and tissue damage in DED by repairing the corneal ECM.[2]

PHASE 2 CLINICAL INSIGHTS

A prior multicenter, double-masked, randomized phase 2 trial (NCT05241470) evaluated ST-100 (20 mg/mL and 50 mg/mL) in 160 patients with signs and symptoms of DED. Participants were treated twice daily, with no serious drug-related adverse events reported.[3] ST-100 achieved the Schirmer Responder Rate endpoint (a ≥ 10-mm increase in tear production) in just 28 days, with no responders in the placebo group. Additional benefits included significant improvements in Schirmer test scores, corneal staining, and ocular discomfort without reliance on artificial tears or antiinflammatory therapies.

MECHANISM OF ACTION

ST-100's therapeutic potential stems from its ability to repair the corneal ECM, particularly collagen, which is crucial for maintaining the corneal nerve bed.[4,5] An intact nerve bed is necessary for parasympathetic stimulation of the lacrimal gland, a key driver of tear production. ST-100 is thought to mitigate protease-induced ECM degradation and inflammatory signaling, preserving both nerve bed function and ocular surface comfort.

Repairing corneal collagen not only restores the structural integrity of the ECM but also interrupts the cycle of inflammation and nerve damage that exacerbates DED. The phase 2 trial results aligned with this mode of action, showcasing rapid and significant improvements in tear production and corneal health.

PHASE 3 AND FUTURE IMPLICATIONS

The ongoing phase 3 trial aims to confirm the findings of the earlier trials in a larger cohort. If successful, ST-100 could become a transformative treatment option for DED, one that offers a novel mechanism of action for patients who do not respond to currently available antiinflammatory medications.

By repairing the ECM and corneal collagen, ST-100 could introduce a structural approach to DED therapy, providing hope for long-term solutions that address the root causes of tear deficiency and inflammation. ■

1. Chattopadhyay S, Murphy CJ, McAnulty JF, Raines RT. Peptides that anneal to natural collagen in vitro and ex vivo. *Org Biomol Chem*. 2012;10(30):5892-5897.
2. Baratta RO, Schlumpf E, Buono BJD, DeLorey S, Calkins DJ. Corneal collagen as a potential therapeutic target in dry eye disease. *Surv Ophthalmol*. 2022;67(1):60-67.
3. Baratta RO, Schlumpf E, Del Buono BJ, DeLorey S, Ousler G, Calkins DJ. A phase 2 trial to test safety and efficacy of ST-100, a unique collagen mimetic peptide ophthalmic solution for dry eye disease. *Ophthalmol Sci*. 2023;4(3):100451.
4. Baratta RO, Del Buono BJ, Schlumpf E, Ceresa BP, Calkins DJ. Collagen mimetic peptides promote corneal epithelial cell regeneration. *Front Pharmacol*. 2021;12:705623.
5. Wareham LK, Holden JM, Bossardet OL, et al. Collagen mimetic peptide repair of the corneal nerve bed in a mouse model of dry eye disease. *Front Neurosci*. 2023;17:1148950.

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