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Acoltremon (Tryptyr) for Dry Eye Disease: A Review of the TRPM8 Agonist Mechanism and Clinical Utility

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ABSTRACT

Dry Eye Disease (DED) is a multifactorial condition characterized by tear film instability, ocular surface inflammation, and neurosensory abnormalities. While the prevalence of DED is rising globally, affecting over 16 million adults in the US alone, treatment options have historically been limited to artificial tears or anti-inflammatory agents with delayed onset of action. Current therapies, such as calcineurin inhibitors and LFA-1 antagonists, effectively target inflammation but often fail to address the neurosensory component of the disease or provide rapid symptomatic relief. The recent FDA approval of Acoltremon (Tryptyr) introduces a first-in-class TRPM8 agonist that specifically targets the eye's natural cooling sensors to stimulate tear production. This viewpoint analyzes the clinical utility of Acoltremon, arguing that its novel mechanism fills a critical gap in the "symptoms without signs" treatment paradigm and offers a distinct advantage in rapidity of onset compared to existing immunomodulators.

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Key Points

- Current DED treatments often suffer from slow onset of action and do not directly address neurosensory dysfunction.
- Acoltremon acts as a TRPM8 agonist, utilizing the eye's cooling sensation pathway to trigger rapid natural tear production.

- Clinical trials demonstrate efficacy as early as Day 1, positioning Acoltremon as a potential first-line option for patients seeking immediate symptomatic relief.

The Unmet Need in Dry Eye Management

Dry Eye Disease (DED) is a growing global burden, with prevalence ranging from 5% to 50% and affecting over 16 million adults in the US alone [2]. Restoration of tear film homeostasis and relief of symptoms remain the primary goals of DED therapy. However, the current standard of care presents significant limitations. Artificial tears provide only transient lubrication without addressing the underlying etiology. While the approval of seven prior drugs has expanded the armamentarium, many, such as cyclosporine and lifitegrast, are characterized by a slow onset of action—often taking weeks to months to show full efficacy—and are associated with compliance-limiting side effects like burning, blurred vision, and dysgeusia [4].

Furthermore, procedures like punctal occlusion preserve existing tears but fail to increase secretion and carry risks of infection or dislodgement. Newer agents like varenicline have introduced nasal stimulation pathways, yet they often induce systemic effects such as sneezing. These limitations underscore a persistent need for a therapy that addresses the pathogenic causes of DED, particularly the neurosensory abnormalities defined by the TFOS DEWS II report [1], while offering a rapid onset of relief.

Acoltremon: A Novel Mechanism of Action

The FDA approval of Acoltremon (Tryptyr) in May 2025 marks the introduction of the first TRPM8 ion channel agonist for DED. Unlike immunomodulators that suppress inflammation, Acoltremon targets the TRPM8 receptors located on the corneal nerve endings, which are responsible for detecting cold sensations [3].

By stimulating these receptors, Acoltremon activates the lacrimal functional unit via a cooling signal, thereby enhancing basal tear secretion and stabilizing the tear film [5]. This mechanism represents a paradigm shift: rather than adding artificial volume or suppressing the immune system, the drug stimulates the eye's innate production capacity. This distinction is clinically relevant for patients with "symptoms disproportionate to signs," as the cooling sensation directly modulates the sensory discomfort often reported in DED.

Clinical Efficacy and Safety Profile

Evidence from the pivotal Phase 3 trials, COMET-2 and COMET-3, highlights the drug's rapid efficacy profile (see Table 1). In these trials involving over 930 patients, Acoltremon 0.003%

ophthalmic solution administered twice daily demonstrated a statistically significant improvement in tear production [5].

Crucially, the primary endpoint—a ≥ 10 mm increase in Schirmer score at Day 14—was achieved by 42.6% (COMET-2) and 53.2% (COMET-3) of patients, compared to only 8.2% and 14.4% in the vehicle groups ($P < 0.0001$) [5]. Unlike anti-inflammatory agents, improvements were observed as early as Day 1 and were maintained through the 90-day trial period. The safety profile was favorable, with instillation site pain being the most frequent adverse event, which is consistent with the drug's mechanism of inducing a cooling sensation [5].

Table 1: Summary of Key Clinical Trials for Acoltremon (AR-15512)

Trial (Phase)	Study Design	N	Regimen	Primary Endpoint (Day 14)	Key Results (Schirmer Score ≥ 10 mm)
COMET-1 (Phase 2b) [3]	Randomized, double-masked, vehicle-controlled	369	0.003% vs. Vehicle (BID)	Tear production (Schirmer) at Day 14	Statistically significant increase in tear production vs. vehicle; validated dose concentration.
COMET-2 (Phase 3) [5, 6]	Randomized, double-masked, vehicle-controlled	460	0.003% vs. Vehicle (BID)	% of eyes with ≥ 10 mm increase in Schirmer score	42.6% (Acoltremon) vs. 8.2% (Vehicle) ($P < 0.0001$)
COMET-3 (Phase 3) [5, 6]	Randomized, double-masked,	470	0.003% vs. Vehicle (BID)	% of eyes with ≥ 10 mm increase in	53.2% (Acoltremon) vs. 14.4% (Vehicle) ($P < 0.0001$)

	vehicle-controlled			Schirmer score	
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Abbreviations: BID, twice daily; N, number of patients.

Comparison with Existing Therapies

Acoltremon occupies a unique niche when compared to the existing landscape (see Table 2 [4,5]). Relative to calcineurin inhibitors (e.g., Restasis, Cequa), it offers a faster onset of action and avoids the "stinging" often associated with T-cell inhibitors [4]. Compared to the nasal spray varenicline, Acoltremon avoids systemic respiratory irritation, and relative to punctal plugs, it actively stimulates production rather than passively conserving tears.

Table 2: Mechanism and Administration of FDA-Approved DED Therapies

Drug	Class	Date of Approval	Mode of Action	Mode of Administration
Cyclosporine (Restasis)	Calcineurin inhibitor	December 23, 2002	Reduces ocular surface inflammation by inhibiting T-cell activation	Topical eye drops (twice daily)
Cyclosporine (Cequa)	Calcineurin inhibitor (nanomicellar)	August 14, 2018	Enhances cyclosporine delivery and anti-inflammatory action via nanomicellar tech	Topical eye drops (twice daily)
Cyclosporine (Vevye)	Water-free cyclosporine solution	May 30, 2023	Lipid-based formulation enhances delivery and efficacy without aqueous solvents	Topical eye drops (twice daily)

Lifitegrast (Xiidra)	LFA-1 antagonist	July 11, 2016	Blocks interaction of LFA-1 and ICAM-1 to reduce ocular surface inflammation	Topical eye drops (twice daily)
Varenicline (Tyrvaya)	Nicotinic acetylcholine receptor agonist	October 15, 2021	Stimulates trigeminal nerve to activate tear secretion via nasal cholinergic pathway	Nasal spray (twice daily)
Loteprednol (Eysuvis)	Corticosteroid	October 26, 2020	Reduces inflammation during DED flares via glucocorticoid receptor binding	Topical eye drops (QID, ≤ 2 weeks)
Perfluorohexyloctane (Miebo)	Semi-fluorinated alkane	May 18, 2023	Reduces tear evaporation by forming a lipid layer on the ocular surface	Topical eye drops (twice daily)

CONCLUSION AND FUTURE DIRECTIONS

Acoltremon represents a significant advancement in the management of DED, offering a targeted approach for patients with tear deficiency and neurosensory symptoms. Its rapid onset and novel mechanism make it a strong candidate for inclusion in national treatment guidelines, particularly for patients who have failed or are intolerant to immunomodulators.

However, clinicians must consider limitations. The drug may be less effective in severe aqueous tear deficiency (e.g., advanced Sjögren's syndrome) where lacrimal gland function is irreversibly compromised. Additionally, the current fixed concentration (0.003%) limits dosage flexibility.

Future studies should evaluate its long-term utility as an adjunct to anti-inflammatory therapy, potentially offering immediate relief while slower-acting agents take effect.

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Author Contributions

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REFERENCES:

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15:276–83. <https://doi.org/10.1016/j.jtos.2017.05.008>
2. Golden MI, Meyer JJ, Zeppieri M, Patel BC. Dry eye disease. In: StatPearls. StatPearls Publishing. 2025. <https://www.ncbi.nlm.nih.gov/books/NBK470411/>. Accessed 6 Feb 2026.
3. Wirta DL, Senchyna M, Lewis AE, et al. A randomized, vehicle-controlled, phase 2b study of two concentrations of the TRPM8 receptor agonist AR-15512 in the treatment of dry eye disease (COMET-1). *Ocul Surf.* 2022;26:166-173. <https://doi.org/10.1016/j.jtos.2022.08.003>
4. Bausch & Lomb Americas Inc. Xiidra (lifitegrast ophthalmic solution) 5% prescribing information. Bausch & Lomb Americas Inc. 2023. <https://pi.bausch.com/globalassets/pdf/packageinserts/pharma/xiidra-prescribing-information.pdf>. Accessed 6 Feb 2026.
5. Alcon Laboratories Inc. Tryptyr (acoltremon ophthalmic solution) 0.003% prescribing information. Alcon. 2025. <https://alcon.widen.net/s/vmmcnwfkq/tryptyr-pi>. Accessed 6 Feb 2026.