Correspondence

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Acoltremon: The first TRPM8 agonist approved for the treatment of dry eye disease

Yang Zhou, Wenzhu Zhang, Fusheng Sun*

Department of Pharmacy, Qingdao Municipal Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong, China.

SUMMARY: Dry eye disease (DED) is a common ocular surface disorder that markedly affects the quality of life (QoL) of patients. Conventional treatments for DED were unable to meet current medical needs. Acoltremon, a transient receptor potential melastatin 8 (TRPM8) agonist, was first approved by the US Food and Drug Administration on May 28, 2025 for treatment of the signs and symptoms of DED. Acoltremon activates TRPM8 receptors, thereby increasing tear production and providing a cooling sensation for symptom relief. Results of clinical trials demonstrated that 0.003% acoltremon markedly alleviated signs and symptoms of DED. Adverse events associated with acoltremon were primarily instillation site pain, and no serious ocular adverse events were noted. Acoltremon has multiple advantages: rapid onset of action, significant alleviation of dry eye signs and symptoms, and favorable safety and tolerability. In summary, the approval of acoltremon represents a new therapeutic perspective on the management of DED.

Keywords: acoltremon, dry eye disease, TRPM8 agonist, cold thermoreceptor modulator, tear production

Dry eye disease (DED) is a multifactorial ocular surface disease that is marked by a loss of tear film homeostasis and that is accompanied by ocular symptoms. The etiologies of DED include tear film instability and hyperosmolarity, inflammation of and damage to the ocular surface, and neurosensory abnormalities (*1*). DED is characterized by insufficient tear production and/or excessive tear evaporation that leads to a series of symptoms including discomfort, in forms such as redness, burning, itching, or a gritty sensation, and impaired vision. This disease predominantly occurs in females and individuals over the age of 50 and it adversely affects a patient's quality of life (QoL) and daily activities (*2,3*). Conventional treatments for DED include lubricants (artificial tears, gels, ointments, and autologous serum), corticosteroids, immunosuppressants (cyclosporine, tacrolimus, and lifitegrast), and a cholinergic agonist (a nasal spray formulation of varenicline) (*4,5*). However, the problems with current conventional treatments mainly include their modest efficacy, unpleasant adverse reactions, and slow onset of action (*6-8*). Thus, development of innovative therapies for the treatment of DED is critical.

Acoltremon (brand name: Tryptyr) is a first-in-class transient receptor potential melastatin 8 (TRPM8) agonist developed by Alcon Laboratories. It was approved by the US Food and Drug Administration on May 28, 2025 for treatment of the signs and symptoms of DED (*9*). TRPM8, a polymodal, calcium-permeable nonselective cation channel, is recognized as a physiological sensor of environmental cold. It is expressed on neurons of the ophthalmic division of the trigeminal nerve in the cornea and eyelid (*10-12*). Studies have demonstrated that TRPM8 plays an important role in regulating tear production and blink rate (*12*). As a cold thermoreceptor modulator, acoltremon activates TRPM8 receptors, thereby increasing tear production and providing a cooling sensation for symptom relief (*10,11*). In addition, due to its cooling stimulation, acoltremon may also benefit patients suffering from neuropathic ocular pain, for which treatment options are currently scarce (*13,14*). Therefore, acoltremon as a TRMP8 agonist has a dual role of both increasing tear production and decreasing ocular discomfort in the treatment of DED (*15*).

Multiple clinical trials have revealed the efficacy and safety of acoltremon for the treatment of DED. A randomized, vehicle-controlled, phase 2b study (COMET-1) evaluated the efficacy of acoltremon (0.0014% and 0.003%, twice a day for 84 days) compared to a vehicle (*15*). Results indicated that 0.003% acoltremon significantly alleviated signs and multiple symptoms of dry eye versus the vehicle. In COMET-2 and COMET-3 (two pivotal phase 3 clinical trials), patients were randomly assigned in equal proportions to receive 0.003% acoltremon or a vehicle

administered twice a day as one drop per eye for 90 days. The primary endpoint of phase 3 clinical trials was the proportion of patients in which an increase in tear production ≥ 10 mm was achieved from pre-drop at the baseline to post-drop on Day 14 according to an unanesthetized Schirmer score. In COMET-2, an increase in tear production ≥ 10 mm from the baseline was achieved in 42.6% of patients treated with acoltremon by Day 14, compared to 8.2% in patients treated with the vehicle (*16*). In COMET-3, an increase in tear production ≥10 mm from the baseline was achieved in 53.2% of patients given acoltremon by Day 14, versus 14.4% in those treated with the vehicle (*16*). The results of clinical studies demonstrated that acoltremon significantly improved tear production in patients with DED ($p < 0.01$) (*16*). Additional data from secondary endpoints showed that acoltremon rapidly increased and consistently maintained tear production compared to the vehicle, beginning on Day 1 and persisting to Day 90 (*17*). In terms of safety, the most frequently noted ocular adverse event in clinical trials with acoltremon was instillation site pain (50%), and no serious adverse events were observed (*16,17*).

Acoltremon is the first TRPM8 agonist approved for the treatment of DED, and it offers clinical advantages because of its rapid onset of action, significant alleviation of dry eye signs and symptoms, and favorable safety and tolerability. Further clinical research needs to be conducted to confirm its real-world efficacy and safety, but the approval of acoltremon offers an innovative and effective approach for treating the signs and symptoms of DED. Overall, the successful development of acoltremon, with its novel mechanisms, is expected to lead to new perspectives on and advances in the management of DED.

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**Address correspondence to:*
Fusheng Sun, Department of Pharmacy, Qingdao Municipal Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong, China.
E-mail: clinphar_slyy@163.com

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