AR-15512, a Novel Topical Drug Candidate for Dry Eye Disease

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Thermoreceptors on the ocular surface play a critical role in the development of dry eye disease (DED). An experimental eye drop called AR-15512, which activates cooling receptors, has been found to provide fast and continuous relief from dry eye symptoms, with minimal side effects. Due to its cold-sensing stimulation, this medication may also help patients experiencing neuropathic ocular pain, for which there are currently limited treatment options available. New prescription therapies for DED are needed, as many patients discontinue conventional treatments due to unpleasant side effects or lack of substantial results.

Keywords

AR-15512, dry eye disease, neuropathic ocular pain, Schirmer testing, thermoreceptors, transient receptor potential melastatin, transient receptor potential melastatin agonist, TRPM8

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AR-15512, a new transient receptor potential melastatin (TRPM8) agonist, has delivered sustained relief of symptoms and improved signs of ocular dryness across numerous clinical trials.[1–6] It was found to increase tear production by activating cooling receptors on the corneal surface.[1] This new mechanism of action is gaining attention in the dry eye space, where traditional treatments have focused on increasing lubrication and anti-inflammatory treatment. This article highlights the current literature on TRPM8 and summarizes the latest research on AR-15512, a new drug candidate for treating DED.

Mechanism of action: Thermoreceptor activation

Formulated as a topical ophthalmic solution, AR-15512 activates TRPM8 receptors on the ocular surface.[1] TRPM8 channels are cold-sensing thermoreceptors located in the cornea and eyelid, and they are expressed on neurons of the ophthalmic branch of the trigeminal nerve.[7,8] These temperature-detecting cation channels respond to ocular surface dryness and hyperosmolarity.[7] TRPM8 channels regulate basal tear levels and blink rate by detecting constant cool temperature stimuli from tear film evaporation.[7,9,10] Stimulation of TRPM8 increases lacrimation and provides an analgesic effect.[9,11] It is suggested that as AR-15512 increases basal tear production, it affects all layers of the natural tear film. Dysfunction of TRPM8 receptors contributes to ocular surface discomfort, while upregulation of TRPM8 decreases pro-inflammatory mediators.[8,9,12] Other TRPM8 agonists have been studied for ophthalmic use and showed comparable results to AR-15512.[8,11] According to deLong et al., AR-15512 is a potent and long-lasting TRPM8 agonist.[13]

Patients with neuropathic ocular pain (NOP) experience symptoms that are disproportionate to their clinical signs.[7] These clinical conditions, often termed 'pain without stain', can be challenging to manage. The TRPM8 receptor is crucial in ocular pain response.[10] Patients with NOP may exhibit cold allodynia, an abnormal pain response to normal cold stimuli.[14] TRPM8 detects both painful cold stimuli and beneficial cooling, such as relief from a cold compress on the eyes or cold artificial tears.[15] There is an upregulation of TRPM8 after corneal nerve ablation, which could contribute to the increased dry eye awareness and excessive watering in the eyes that patients experience after ophthalmic surgery.[16]

It has been shown that blocking the TRPM8 receptor can also be a valuable therapeutic approach for treating ocular surface disease.[17,18] A recent analysis by Ran et al. showed that TRPM8 knock-out mice had faster corneal epithelium healing than wild-type mice.[17] Consequently, the TRPM8 knock-out mice showed worse corneal opacification and thickening.[17] Researchers concluded that TRPM8 function is essential for corneal homeostasis.[17] Further investigation is needed to

understand the activation versus suppression of TRPM8 in the treatment of both DED and NOP.

Safety and efficacy of AR-15512

Aerie Pharmaceuticals, now acquired by Alcon, has conducted a series of clinical studies, which began in 2020 to study AR-15512 for treating DED. Alcon has previously stated plans to submit a new drug application for AR-15512 in 2024.[6]

COMET-1 (A Phase 2b Study Evaluating the Safety and Efficacy of AR-15512 Ophthalmic Solution for the Treatment of Dry Eye Disease; ClinicalTrials.gov identifier: NCT04498182), a phase IIb, randomized, quadruple masked, vehicle-controlled trial, compared two concentrations of AR-15512 (0.003% and 0.0014%) with a placebo for improving the signs and symptoms of DED in patients with moderate-to-severe DED.[1,5] Masked subjects (n=369, 1:1:1) used one drop of active ingredient or vehicle twice daily for 12 weeks. On day 84, patients using 0.003% treatment showed statistically significant improvement in their scores across multiple dry eye symptom questionnaires. Several quality-of-life measures were tracked during the study, such as depression, ability to drive, watching TV and reading. Marked improvements in the 0.003% treatment group were noted after only 14 days. There was no difference in the anaesthetized Schirmer test on day 28 or day 84 between all the three treatment groups. However, both treatment arms found a substantial increase in unanaesthetized Schirmer testing on day 1 and day 14. The distinction between anaesthetized and unanaesthetized Schirmer test results is thought to be due to the drug's mechanism of action, which requires trigeminal nerve transmittance to signal tear production. Ocular surface staining was significantly improved in the 0.003% treatment group on day 14 and day 84, and hyperaemia improved considerably on day 84. Anterior segment optical coherence tomography (OCT) measurements of tear meniscus height also showed a significant increase following the application of 0.003% AR-15512. The medication was safe and well tolerated. Burning and stinging upon instillation were the most frequently reported side effects, with most patients rating the discomfort as mild; only two participants in the 0.003% AR-15512 group discontinued due to instillation-site discomfort.

The treatment group in COMET-1 with a lower concentration of 0.0014% did not show statistically significant improvement in many signs or symptoms, so the COMET-2 (A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease; ClinicalTrials.gov identifier: NCT05285644) (n=465) study moved forward with the higher concentration.[2,3] This phase III, randomized, quadruple masked, vehicle-controlled, multi-centre trial further demonstrated positive results in both the safety and efficacy of 0.003% AR-15512, dosed twice daily for 90 days.[2] The study met its primary end-point of ≥10 mm increase in unanaesthetized Schirmer strip test measured at 14 days.[2] The COMET-3 trial (A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease; ClinicalTrials.gov identifier: NCT05360966) (n=467) was identical to the COMET-2 trial and achieved the same success in reaching the primary end-point.[2] In both studies, there were no serious adverse events.[2] Formal results have yet to be published.

Conclusion

Both patients and clinicians are seeking new treatment options that can quickly alleviate dry eye suffering. Targeting thermoreceptors presents a unique approach to treating ocular surface disease, one that eye care providers may continue to see with the ongoing drug development. The new drug candidate, AR-15512, has been successful in improving both functional and clinical signs of DED. AR-15512 fills a therapeutic gap by providing a rapid onset of action, convenient twice-daily dosing and minimal side effects. Patients with a history of ophthalmic surgery or those who have experienced symptoms disproportionate to their corneal staining may especially benefit from TRPM8 activation due to corneal nerve injury. Patients often discontinue current prescription-strength dry eye medications because of intolerable side effects or insufficient rapid results. This novel formulation could become first-line prescription therapy due to its favourable side effects and speed of results. If AR-15512 is approved and brought to market, it would represent a revolutionary mechanism for treating DED. ❑

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