# Efficacy, Safety, and Acceptability of a Lipid-Based Artificial Tear Formulation: A Randomized, Controlled, Multicenter Clinical Trial

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## ABSTRACT

**Purpose:** Dry eye disease is highly prevalent worldwide, causing discomfort and visual disturbances that can limit basic activities such as reading and driving. Although artificial tears represent first-line therapy, there is a paucity of published controlled clinical trials. The present study compared the efficacy, clinical safety, and acceptability of 2 multicomponent, lipid-based tear formulations (ADV1 and ADV2) to those of an existing lipid-based tear formulation (DET) in patients with signs and symptoms of dry eye disease.

**Methods:** This 3-month, multicenter, double-masked study was conducted in patients with dry eye symptoms, reduced tear break-up time (TBUT), and ocular surface damage. Patients were randomized to receive 1 of 2 lipid-based tear formulations containing carboxymethylcellulose, glycerin, polysorbate 80, and emulsified lipid (ADV1 or ADV2) or DET, and instilled 1 to 2 drops per eye at least twice daily. The primary end point was the mean change from baseline in Subjective Evaluation of Symptom of Dryness score at day 90 to determine noninferiority of the 2 ADV formulations versus DET. Secondary end points included Ocular Surface Disease Index (OSDI) score, TBUT, ocular surface staining, and tolerability.

**Findings:** Of 288 randomized patients, 256 completed the study. All 3 groups showed improvement in symptoms, and the 2 lipid-based formulations were noninferior to DET in reducing the severity of symptoms of dryness at 90 days. Of the 3 treatment groups, the ADV2 group had the greatest improvements in TBUT and OSDI. Significant improvements in mean tolerability scores for comfort, soothing, burning/stinging, and discomfort were observed in the ADV2 group versus the DET group at 90 days. Treatment-related adverse events were reported in 13 patients (13.4%) receiving ADV1, 8 (8.4%) receiving ADV2, and 21 (21.9%) receiving DET. Four patients (4.1%) in the ADV1 group and 2 (2.1%) in the ADV2 group discontinued owing to an adverse event compared with 14 (14.6%) receiving DET.

**Implications:** In these patients with dry eye symptoms, ADV2 was an effective and relatively well-tolerated artificial tear for first-line therapy and should be considered as a treatment option for dry eye, especially in those patients who would benefit from a lipid-based formulation in addition to lubrication. https://clinicaltrials.gov/ct2/show/NCT01010282. (*Clin Ther*. 2015;37:858–868) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** artificial tears, carboxymethylcellulose, dry eye syndrome, lipid layer, osmoprotection, tear film.

## INTRODUCTION

Dry eye disease is highly prevalent worldwide and is one of the most frequent patient complaints encountered in clinical eye care.[1–5] Although more common in older adults, dry eye occurs in younger patients as well. Dry eye can be exacerbated by work and activity patterns that involve prolonged and demanding visual tasks with computers, smartphones, and other devices.[3] The clinical relevance of dry eye disease is emphasized by its significant impact on the quality of life of affected patients. Symptoms of ocular discomfort include dryness, burning, stinging, photophobia, foreign body sensation, and contact lens intolerance. These

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symptoms may affect basic daily activities, such as reading, driving, and working with computers.[6]

Dry eye disease is characterized by a change in the quantity and/or quality of the tear film that leads to insufficient wetting and lubrication of the exposed ocular surface. In the case of altered lipid secretion from the meibomian glands, dry eye also can be caused by an increased rate of evaporation. Excessive evaporation results in instability of the tear film, with subsequent desiccation and damage to the ocular surface and related symptoms.[7,8]

For eye care clinicians, dry eye disease has long been a challenging condition to address.[5] Tear supplementation with ocular lubricants (artificial tears) is considered the first-line therapy and is often the only therapy used in mild to moderate disease.[9–11] However, the effects of many of the available products have not been evaluated in controlled clinical trials. The majority of artificial tear formulations contain soluble polymeric lubricants, such as cellulose ethers, carbomers, polyvinyl alcohols, polyvinyl pyrrolidones, and sodium hyaluronate, as the therapeutic ingredients.[1] Formulations have been developed to moisten and lubricate the ocular surface, but they may not address evaporative dry eye.

Previously published studies have reported that castor oil has beneficial properties when added to artificial tear preparations. The major component of castor oil, ricinoleic acid, an unsaturated omega-9 fatty acid with a hydroxyl group, allows the castor oil to spread readily over the aqueous component of the tear film, reducing evaporation and increasing tear film stability.[1,12,13] However, blurred vision and a viscous sensation have been reported with the use of artificial tears containing castor oil.[10]

Two investigational, multicomponent, lipid-containing artificial tear formulations have been designed with the aim of maintaining the efficacy of the earlier developed, lipid-based artificial tears while improving safety, tolerability and patients' acceptability. Both formulations (ADV1 and ADV2*) contain carboxymethylcellulose (CMC), which provides lubrication, and castor oil, which retards tear evaporation, while ADV1 also contains olive oil. In addition, these products contain glycerin, L-carnitine, and erythritol to protect the ocular surface from hyperosmotic stress.[14] The objective of the present multicenter, double-masked, randomized clinical trial was to compare the efficacy, safety, tolerability, and acceptability of the 2 new lipid-based formulations (ADV1 and ADV2) to those of an existing lipid-based tear formulation (DET†) in patients with signs and symptoms of dry eye disease.

## PATIENTS AND METHODS

Patients aged 18 years of age or older, with a history of dry eye signs and symptoms for a minimum of 3 months, were enrolled at 1 of 13 sites in the United States. Inclusion and exclusion criteria were designed for enrolling primarily patients with mild to moderate dry eye in whom monotherapy with an artificial tear would be considered appropriate by most clinicians. Criteria included a minimum score of 2 on the Subjective Evaluation of Symptom of Dryness questionnaire,[15] 3 consecutive measures of tear break-up time (TBUT) $<10$ seconds, and ocular surface staining observed in at least 1 zone of the cornea (with fluorescein) or conjunctiva (with Lissamine Green [Rose Stone Enterprises, Alta Loma, California]), using a modified National Eye Institute grading scheme.[16,17] Patients were excluded if they were contact lens wearers; using other ophthalmic medications; and had a recent change in use of a systemic medication, or a history of ophthalmic surgery within 1 year, or signs of severe dry eye including a Schirmer test result of $\leq 2$ mm/5 min or grade 5 staining in any zone of the cornea or conjunctiva.

The trial was conducted in compliance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Institutional review board approval was obtained at each investigational site, and informed consent was obtained from each patient before data collection. The trial is registered at https://clinicaltrials.gov/ct2/show/NCT01010282.

### Study Treatments

Using a computer algorithm, patients were randomized, within each site on a 1:1:1 basis, to receive 1 of 2 artificial tear formulations—ADV1 or ADV2—or DET (Table I). Masked treatment was allocated to the patients by an automated system and dispensed to patients on days 1 (baseline), 30, and 60. Patients were instructed to instill 1 to 2 study

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