Clinical Optometry

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Patient Experience with ABBV-444, a Proof-of-Concept Study for a Novel Artificial Tear with Trehalose and Sodium Hyaluronate for Dry Eye Symptoms

Milton M Hom[1], Omar Ladhani[2], Zuoyi Zhang[2], Haixia Liu[3], Sadhana Sonparote[2], Charlotte C Dancey[3]

[1]Canyon City Eyecare, Azusa, CA, USA; [2]AbbVie, North Chicago, IL, USA; [3]AbbVie, Irvine, CA, USA

Correspondence: Charlotte C Dancey, AbbVie, 2525 Dupont Drive, Irvine, CA, USA, Tel +1 (949) 386 6594, Email charlotte.dancey@abbvie.com

Purpose: Dry eye disease (DED) causes discomfort and potential damage to the surface of the eye, commonly managed with artificial tears. We assessed symptom relief, tolerability, and patient experience of a novel carboxymethyl-cellulose–based artificial tear formulation with trehalose and sodium hyaluronate (ABBV-444) in patients with DED.

Methods: This open-label, single-arm, single center study enrolled adult patients with baseline Ocular Surface Disease Index (OSDI) scores of ≥18 and ≤65. Patients were instructed to use ABBV-444 as often as needed but at least twice a day for 30 days. The primary endpoint was change from baseline in OSDI score at Day 30. Secondary endpoints were onset of action (change from baseline in current symptom survey [CSS] visual analog scale [VAS] scores over 5 minutes post administration on Day 1) and patients' experience (change from baseline in Patient Eye Drop Experience [PEDE] survey VAS scores at Day 30). Outcomes were assessed in the per-protocol (PP) population using descriptive statistics. A paired *t*-test was performed to calculate *P*-values.

Results: A total of 34 patients were included in the PP population. DED severity, measured by OSDI, significantly decreased by a mean (standard deviation; SD) score of 6.8 (15.0) points from baseline to Day 30 (P=0.006). Patients showed significant symptom improvement as early as 30 seconds after application, with mean (SD) CSS changes from baseline of −3.3 (10.3) points at 30 seconds (P=0.03) and −10.1 (10.6) points at 5 minutes post-dose (P<0.001). No adverse events were reported. PEDE scores averaged between 76.4 (36.7) and 85.7 (21.0) at Day 30.

Conclusion: Continuous daily treatment with ABBV-444 reduced DED symptom severity over 30 days and demonstrated rapid onset of action within 30 seconds post administration. These results suggest that ABBV-444 is a viable therapy for DED symptoms and support further investigation of longer-term treatment in multicenter trials.

Keywords: artificial tears, carboxymethylcellulose, dry eye disease, trehalose

Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface, characterized by the loss of homeostasis of the tear film[1] and symptoms such as ocular pain and discomfort, blurred vision, and poor sleep quality.[2] Dry eye symptoms can reduce quality of life by impacting individuals' ability to participate in work and other daily actions, including reading and driving.[3] DED is thought to be caused by tear film instability and hyperosmolarity, which lead to inflammation, damage of the ocular surface, and neurosensory abnormalities.[1] The 2013 National Health and Wellness Survey found the prevalence of diagnosed DED in the US adult population to be 6.8%, with an additional 2.5% of the population believed to have undiagnosed DED.[4] The incidence of DED increases with age, with an estimated prevalence of 3.4% of individuals aged 18–49, 11.3% of those aged ≥50 years, and 18.6% of those aged ≥75 years.[4] There are also suggestions that the prevalence of DED is increasing in younger populations, with the trend hypothesized to be associated with a range of factors, such as extended screen usage.[5–7] As a result, there has been increasing interest in early-onset DED.

Received: 14 August 2024
Accepted: 22 January 2025
Published: 12 February 2025

Artificial tears are often used as the primary therapy in patients with mild-to-moderate DED, and alone or in conjunction with pharmacotherapy and/or punctal plug surgery in patients with moderate-to-severe DED.[8,9] Artificial tears provide lubrication and protection of the ocular surface, as well as relief from symptoms such as burning, irritation, and discomfort.[10] These formulations typically contain water-soluble polymers that increase the viscosity and enhance retention time of the solution on the ocular surface.[8] One such polymer is sodium carboxymethyl cellulose (Na CMC), which is widely used in artificial tears as a viscosity agent[9] that binds to the corneal surface, thereby increasing tear retention time and promoting corneal wound healing.[11] However, some patients continue to experience DED symptoms while using this therapy.[12] Development of new formulations with greater efficacy is necessary to improve the treatment landscape for patients with DED.

Refresh Relieva® (AbbVie, US) is a multi-ingredient, preservative-free, Na CMC-based eye drop formulation. In a multicenter, double-masked, randomized, parallel-group, clinical comparison study, Refresh Relieva was found to be effective in reducing symptoms in patients with mild-to-severe DED.[13] The overall incidence of treatment-related adverse events (AEs) in this study was low, with eye irritation the most common ocular AE reported.[13]

ABBV-444 (Refresh Relieva PF Xtra™), is a novel artificial tear formulation based on that of Refresh Relieva, with the addition of trehalose. Trehalose is a natural disaccharide that, in combination with hyaluronic acid (HA), has been shown to reduce tear osmolarity and inflammation, protect against desiccation, and improve corneal epithelial cell survival.[14–17] The addition of trehalose to the formulation of ABBV-444 (making ABBV-444 the only artificial tears with CMC-HA and trehalose to date) is theorized to further enhance patient comfort. The objective of this study was to assess symptom relief, tolerability, and the overall patient experience of ABBV-444.

Materials and Methods

Study Design

As this was a proof-of-concept study, a single-center design was chosen. This single-arm, single-center, open-label study (NCT05878067) evaluated the subjective experience of patients with DED during treatment with ABBV-444 (Figure 1). Patients were instructed to administer 1–2 drops of ABBV-444 in each eye as needed, with a minimum dosage of twice daily. Patients were surveyed during study visits at screening, baseline (Day 1), Day 14, and Day 30. The study was conducted in accordance with the Declaration of Helsinki and approved by the Advarra Institutional Review Board prior to contact with patients. Eligible patients provided written informed consent and relevant patient information was recorded per standard of care into the institution's patient health record management system.

Patients

This study included patients who were ≥18 years old, had used artificial tears for dry eyes within the past year, had an Ocular Surface Disease Index (OSDI) score of ≥18 and ≤65 (based upon a 0 to 100 scale) at screening and baseline visits, and had three consecutive Tear Break Up Time tests ≤10 seconds in at least one eye at screening visit. Patients were also eligible if they had Grade 1 to 4 (modified National Eye Institute Grid, score range = 0 to 5) staining in at least one area of the cornea (five areas examined) or conjunctiva (five areas examined) that was related to DED in at least one eye at both screening and baseline visits.

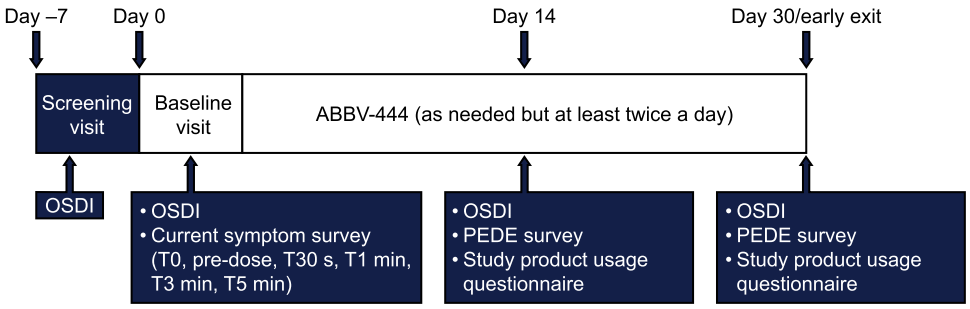

Figure 1 Study Design.
Abbreviations: OSDI, Ocular Surface Disease Index; PEDE, Patient Eye Drop Experience; T, time point.

https://doi.org/10.2147/OPTO.S490732

Patients with uncontrolled severe systemic disease that would put the patient's safety at risk, or an ocular condition in at least one eye that would prevent or confound protocol-specified assessments were excluded. Those currently using systemic medications that may affect tear film, topical ocular medications within 2 weeks of the screening visit, or receiving current treatment with an intraocular pressure-lowering medication, any form of topical ophthalmic cyclosporine, or artificial tears were also excluded. Full eligibility criteria are shown in Supplementary Table 1.

Study Endpoints

The primary endpoint of this study was the change from baseline in OSDI score at Day 30. Secondary endpoints were change from baseline in current symptom survey (CSS) scores over 5 minutes post-administration on Day 1 and Patient Eye Drop Experience (PEDE) scores at Day 30. Exploratory endpoints included the change from baseline in OSDI scores and PEDE scores, both recorded at Day 14.

Surveys

DED symptom severity was assessed using the validated OSDI questionnaire.[18] Patients were asked to record their responses to 12 questions describing common DED symptoms. These responses were then used to calculate an overall OSDI score of 0–100, with higher scores indicating more severe disease.

A CSS visual analog scale (VAS) survey was used to evaluate the onset of action of eye drops in terms of relief of symptoms. A 13-question PEDE VAS survey was used to evaluate patients' short- and long-term subjective experience of symptom relief and tolerability (with a higher value indicating a better experience). Both the CSS and PEDE surveys were assessed using a 0 to 100-point VAS. Patients were instructed to mark a vertical line on the anchored VAS that best described their agreement with the statements within the questionnaire; these responses were then converted to a numerical value using Lumanity® software (Lumanity Ltd, Bethesda, MD).

A product usage questionnaire was used to assess patient compliance with study treatment. Patients completed the OSDI questionnaire at the screening visit, baseline visit (Day 1), and on Days 14 and 30. The CSS survey was administered pre-dose and at 30 seconds, 1 minute, 3 minutes, and 5 minutes post-dose on Day 1. The PEDE survey and study product usage questionnaire were completed on Days 14 and 30.

Statistical Analysis

The clinical trial site mailed the completed surveys back to Lumanity Ltd for data entry and analysis. VAS surveys (CSS and PEDE) used the average score of researchers' individual measurements for data entry. Surveys not conducted using a VAS (OSDI and the Study Product Usage Questionnaire) had the data entered manually by one researcher and quality checked against the original source by a second researcher.

All analyses were performed in the per-protocol (PP) population, defined as all patients who were treated with ABBV-444 and remained on treatment for the entire study period without significant protocol deviations, using Microsoft Excel software. The PP population was used because some patients in the intent-to-treat (ITT) population did not meet all the selection criteria for the study. Patient demographics, characteristics, and health information were summarized and reported in aggregate. All survey data were analyzed descriptively. Arithmetic mean, median, standard deviation (SD), standard error of the mean, interquartiles, minimum, and maximum were used for the description of the data. Where data points were missing, the mean of the data set without the missing values was calculated and imputed. A paired *t*-test was performed to calculate *P*-values.

Results

Study Disposition

A total of 40 patients were enrolled and received at least one dose of ABBV-444 and were included in the ITT population (Figure 2). Of the ITT population, 34 patients (85%) completed the study and were included in the PP population, while six patients (15%) were excluded from the PP population due to discontinuation of treatment (2, 5%) and protocol deviations (4, 10%). Of the four patients excluded due to protocol deviations, one patient had a baseline OSDI score <18 and three had a baseline OSDI score >65. Due to these discrepancies, the PP population is presented here.

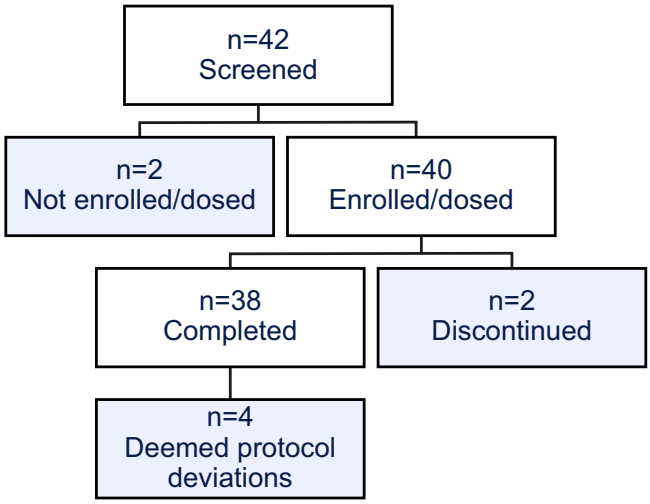

Figure 2 Study Disposition.
Notes: Of the four patients excluded from the PP population, one patient had a baseline OSDI score < 18 and three patients had a baseline OSDI score >65.

Patient Demographics

Of the 34 patients in the PP population, 21 (61.8%) were female, the median age was 37.5 years (range 18–74), and baseline OSDI scores were moderate in 10 patients (29.4%) and severe in the remaining 24 patients (70.6%) (Table 1).

Table 1 Patient Demographics

	PP Population (n=34)
Age (in years)	
Mean (SD)	37.8 (15.2)
Median	37.5
Range	18–74
Sex, n (%)	
Female	21 (61.8)
Male	13 (38.2)
Race, n (%)	
White	32 (94.1)
Black or African American	1 (2.9)
Other[a]	1 (2.9)
Ethnicity, n (%)	
Hispanic/Latino	32 (94.1)
Not Hispanic/Latino	2 (5.9)
Baseline OSDI score, n (%)	
Mild (13–22)	0
Moderate (23–32)	10 (29.4)
Severe (33–100)	24 (70.6)

Note: [a]One patient selected "Other" and specified "Native American."
Abbreviations: OSDI, Ocular Surface Disease Index; PP, per-protocol; SD, standard deviation.

https://doi.org/10.2147/OPTO.S490732

Dosing

Patients reported using ABBV-444 eye drops an average (SD) of 2.3 (0.7) times per day at Day 14, and 2.8 (1.5) times per day at Day 30.

Safety

No AEs were reported during the course of the study (Table 2).

Efficacy and Patient Experience

A significant reduction in DED symptom severity following administration of ABBV-444 was observed at Day 14 and Day 30, with mean (SD) changes from baseline in OSDI score of −8.1 (15.9) and −6.8 (15.0) points, respectively (P=0.002 and P=0.006) (Figure 3). Significant reductions in CSS scores following the first dose of ABBV-444 occurred in a time-dependent manner over the 5-minute period, with mean (SD) changes from baseline CSS score of −3.3 (10.3), −6.3 (10.2), −9.1 (10.7), and −10.1 (10.6) points from time point (T)0–30 seconds (P=0.03), T0–1 minute (P<0.001), T0–3 minutes (P<0.001), and T0–5 minutes (P<0.001) respectively, post dose (Figure 4). The PEDE survey question on continued comfort from eye dryness had the highest mean (SD) scores on Days 14 and 30, with ratings of 81.2 (21.3) and 85.7 (21.0), respectively, at 30 minutes recall. The survey question pertaining to the study drops not causing stinging or burning had the lowest mean (SD) scores on Days 14 and 30, with ratings of 57.1 (42.9) and 76.4 (36.7), respectively, at 5 minutes post-dose (Figure 5).

Discussion

Artificial tears are the primary treatment option for patients with DED due to their accessibility,[9] ease of use, and ability to provide immediate relief of symptoms. The majority of patients with DED are prescribed artificial tear formulations,[9,19] and so patients' subjective experience is an important measure of efficacy. The addition of trehalose to ABBV-444 presents a new formulation with the goal of maintaining symptom relief while improving patient comfort.

Table 2 Summary of Dosage and Safety from the Product Usage Questionnaire

	PP Population (n=34)
Day 14	
On average, how many times did you administer the eye drops per day?	
Mean (SD)	2.3 (0.7)
Median	2.0
Range	1.0–4.5
Day 30	
On average, how many times did you administer the eye drops per day?	
Mean (SD)	2.8 (1.5)
Median	2.0
Range	1.5–6.5
AEs, n	
Any AEs	0
Treatment-related AEs	0
Serious AEs	0
AEs leading to discontinuation	0

Abbreviations: AE, adverse event; PP, per-protocol; SD, standard deviation.

https://doi.org/10.2147/OPTO.S490732

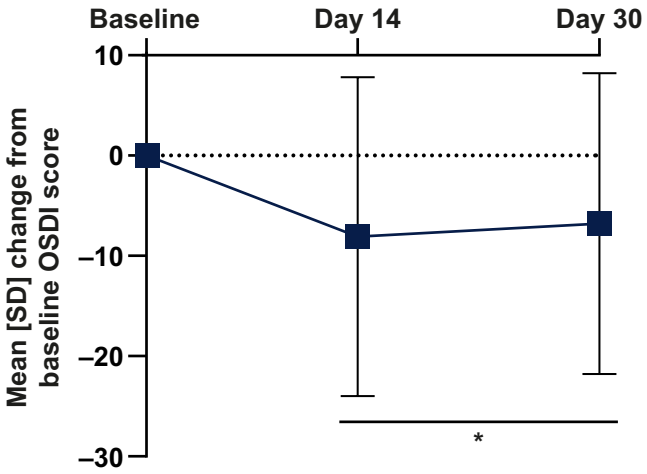

Figure 3 Change from Baseline in OSDI Score from Day 14 to Day 30.
Notes: Error bars show the SD. *P<0.05.
Abbreviation: OSDI, Ocular Surface Disease Index; SD, standard deviation.

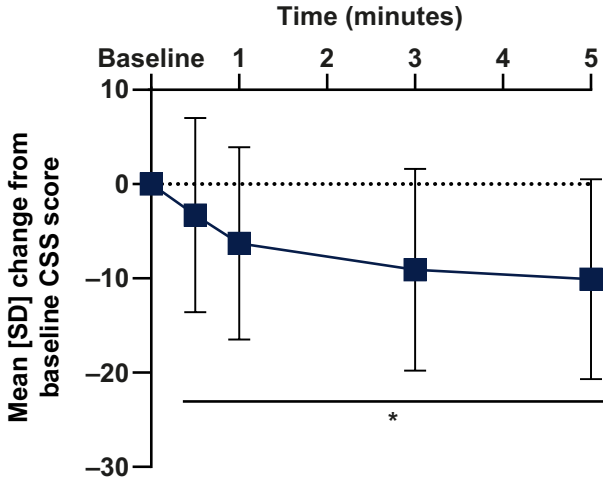

Figure 4 Change from Baseline in CSS Score from 0–5 Minutes Post Administration.
Notes: Error bars show the SD. *P<0.05.
Abbreviations: CSS, current symptom survey; SD, standard deviation.

Our study used multiple subjective measures to comprehensively evaluate the efficacy, patient experience, and eye drop experience of ABBV-444 in patients with DED.

In this descriptive study, use of ABBV-444 at least twice daily was associated with a significant reduction in symptom severity and a positive patient experience among individuals with DED. ABBV-444 demonstrated an onset of action as early as 30 seconds in reducing symptoms of DED. Patients reported consistently improved experiences in PEDE survey questions on Day 30 compared with Day 14. The best patient experience recorded was related to continued comfort from eye dryness, and the lowest PEDE score recorded was related to stinging and burning in the eyes. ABBV-444 eye drops showed a favorable tolerability and safety profile, notably with no AEs observed. Clinical trials of other Refresh formulations of artificial tears showed they were well tolerated, with eye irritation reported as the most common AE.[13]

The continued DED symptom relief reported in this study is consistent with the results of previous studies investigating eye drop formulations containing CMC-HA or trehalose plus HA.[20,21] In a study of 384 patients with

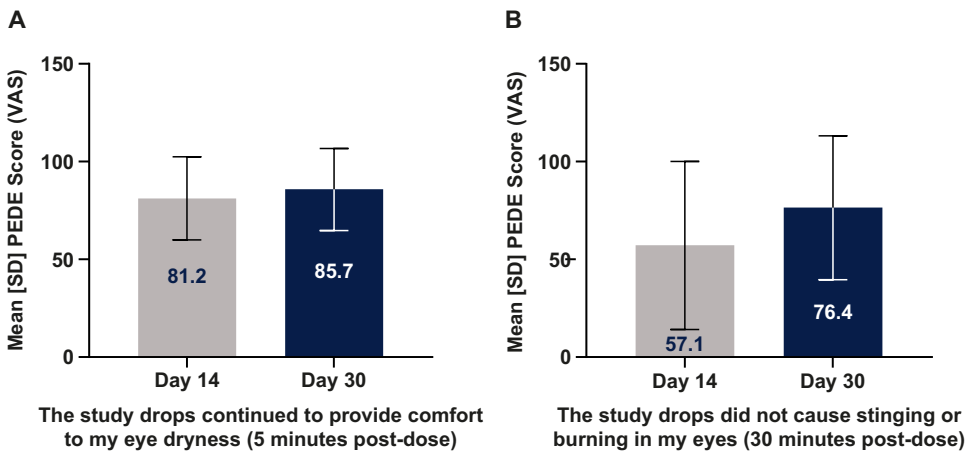

Figure 5 PEDE Scores for (**A**) the Lowest Scoring Question (recorded at 5 minutes) and (**B**) the Highest Scoring Question (recorded at 30 minutes) on Days 14 and 30.
Notes: Error bars show the SD.
Abbreviations: PEDE, Patient Eye Drop Experience; SD, standard deviation; VAS, visual analog scale.

DED who were examined using a Schirmer's test to measure ocular tear production, patients treated with 0.1% sodium hyaluronate Hylotears containing trehalose had a significantly higher mean Schirmer's test value compared with patients receiving the standard formulation ($P<0.001$) after 8 weeks, indicating improved tear production.[22] In a separate study, 273 women with DED were evaluated using OSDI scoring. Patients receiving trehalose and HA-containing eye drops reported a significant reduction from baseline in DED symptoms ($P<0.0001$).[21] In other prior studies, the addition of trehalose has been shown to improve tear film instability in patients undergoing cataract surgery[23,24] and CMC-HA has enhanced recovery of the ocular surface in patients post-laser assisted in situ keratomileusis (LASIK®).[25]

As is typical for descriptive studies, interpretation of this study is subject to a number of limitations. These include its uncontrolled, single-group, single-center design, the small number of included patients, the exclusion of six patients from the PP population, and the subjective nature of the patient experience questionnaires.

In conclusion, this proof-of-concept patient-experience study demonstrated that ABBV-444 eye drops are an effective short-term therapy for symptom relief in patients with DED, reducing DED symptoms and severity over a 30-day period. Patients reported rapid symptomatic relief after administration and a favorable eye drop experience. Additionally, ABBV-444 was well tolerated. To evaluate the longer-term effects of ABBV-444 in reducing both the symptoms and signs of DED in patients, a larger patient population across multiple clinical centers with a longer duration is currently underway.

Abbreviations

AE, adverse event; CMC, carboxymethyl cellulose; CMC-HA, carboxymethylcellulose-hyaluronic acid; CSS, current symptom survey; DED, dry eye disease; HA, hyaluronic acid; ITT, intent-to-treat; LASIK, laser assisted in situ keratomileusis; NA CMC, sodium carboxymethyl cellulose; OSDI, Ocular Surface Disease Index; PEDE, patient eye drop experience; PP, per-protocol; SD, standard deviation; VAS, visual analog scale.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for

publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Acknowledgments

AbbVie and the authors thank the patients, study sites, and investigators who participated in this clinical trial. Allergan (prior to its acquisition by AbbVie) funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, reviewing, and approval of this publication. No honoraria or payments were made for authorship. Medical writing and editorial support were provided by Jack Roweth, MSc, and Laura McArdle, BA, of Spark (a division of Prime, New York, USA), funded by AbbVie.

Funding

This study was funded by AbbVie.

Disclosure

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, reviewing, and approval of this publication. No honoraria or payments were made for authorship. Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: MMH is a consultant for AbbVie/Allergan, Bausch, Lenz, Viatris, Ocuphire, AstaReal, Tarsus, and Thea. OL is a former employee of AbbVie, currently employed by Kura Oncology, and may hold AbbVie stock. ZZ, HL, SS, and CCD are employees of AbbVie and may hold AbbVie stock.

References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008
2. Guo OD LW, Akpek EK. The negative effects of dry eye disease on quality of life and visual function. *Turk J Med Sci*. 2020;50(SI–2):1611–1615. doi:10.3906/sag-2002-143
3. Uchino M, Schaumberg DA. Dry eye disease: impact on quality of life and vision. *Curr Ophthalmol Rep*. 2013;1(2):51–57. doi:10.1007/s40135-013-0009-1
4. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol*. 2017;182:90–98. doi:10.1016/j.ajo.2017.06.033
5. Muntz A, Turnbull PR, Kim AD, et al. Extended screen time and dry eye in youth. *Cont Lens Anterior Eye*. 2022;45(5):101541. doi:10.1016/j.clae.2021.101541
6. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15(3):334–365. doi:10.1016/j.jtos.2017.05.003
7. Stapleton F, Velez FG, Lau C, Wolffsohn JS. Dry eye disease in the young: a narrative review. *Ocul Surf*. 2024;31:11–20. doi:10.1016/j.jtos.2023.12.001
8. Aragona P, Giannaccare G, Mencucci R, Rubino P, Cantera E, Rolando M. Modern approach to the treatment of dry eye, a complex multifactorial disease: a P.I.C.A.S.S.O. board review. *Br J Ophthalmol*. 2021;105(4):446–453. doi:10.1136/bjophthalmol-2019-315747
9. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575–628. doi:10.1016/j.jtos.2017.05.006
10. Semp DA, Beeson D, Sheppard AL, Dutta D, Wolffsohn JS. Artificial tears: a systematic review. *Clin Optom*. 2023;15:9–27. doi:10.2147/OPTO.S350185
11. Garrett Q, Simmons PA, Xu S, et al. Carboxymethylcellulose binds to human corneal epithelial cells and is a modulator of corneal epithelial wound healing. *Invest Ophthalmol Vis Sci*. 2007;48(4):1559–1567. doi:10.1167/iovs.06-0848
12. Kim M, Lee Y, Mehra D, Sabater AL, Galor A. Dry eye: why artificial tears are not always the answer. *BMJ Open Ophthalmol*. 2021;6(1):e000697. doi:10.1136/bmjophth-2020-000697
13. Simmons PA, Liu H, Carlisle-Wilcox C, Vehige JG. Efficacy and safety of two new formulations of artificial tears in subjects with dry eye disease: a 3-month, multicenter, active-controlled, randomized trial. *Clin Ophthalmol*. 2015;9:665–675. doi:10.2147/OPTH.S78184
14. Laihia J, Kaarniranta K. Trehalose for ocular surface health. *Biomolecules*. 2020;10(5):809. doi:10.3390/biom10050809
15. Wozniak PA, Schmidl D, Bata AM, et al. Effect of different lubricant eye gels on tear film thickness as measured with ultrahigh-resolution optical coherence tomography. *Acta Ophthalmol*. 2017;95(4):e307–e313. doi:10.1111/aos.13342
16. Chen W, Zhang X, Liu M, et al. Trehalose protects against ocular surface disorders in experimental murine dry eye through suppression of apoptosis. *Exp Eye Res*. 2009;89(3):311–318. doi:10.1016/j.exer.2009.03.015
17. Labetoulle M, Benitez-Del-Castillo JM, Barabino S, et al. Artificial tears: biological role of their ingredients in the management of dry eye disease. *Int J Mol Sci*. 2022;23(5):2434. doi:10.3390/ijms23052434

18. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol*. 2000;118(5):615–621. doi:10.1001/archopht.118.5.615
19. Swanson M. Compliance with and typical usage of artificial tears in dry eye conditions. *J Am Optom Assoc*. 1998;69(10):649–655.
20. Aragona P, Benítez-Del-Castillo JM, Coroneo MT, et al. Safety and efficacy of a preservative-free artificial tear containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized, controlled, multicenter 3-month study. *Clin Ophthalmol*. 2020;14:2951–2963. doi:10.2147/OPTH.S256480
21. Mateo-Orobia AJ, Del Prado Sanz E, Blasco-Martinez A, Pablo-Julvez LE, Farrant S, Chiambaretta F. Efficacy of artificial tears containing trehalose and hyaluronic acid for dry eye disease in women aged 42-54 versus >/= 55 years. *Cont Lens Anterior Eye*. 2023;46(4):101845. doi:10.1016/j.clae.2023.101845
22. Morya AK, Solanki K, Prakash S, Samota M, Gupta A. Randomized controlled trial of trehalose: an efficient autophagic bioprotectant in the management of dry eye disease. *Taiwan J Ophthalmol*. 2020;11(2):161–167. doi:10.4103/tjo.tjo_58_20
23. Cagini C, Torroni G, Mariniello M, Di Lascio G, Martone G, Balestrazzi A. Trehalose/sodium hyaluronate eye drops in post-cataract ocular surface disorders. *Int Ophthalmol*. 2021;41(9):3065–3071. doi:10.1007/s10792-021-01869-z
24. Caretti L, La Gloria Valerio A, Piermarocchi R, et al. Efficacy of carbomer sodium hyaluronate trehalose vs hyaluronic acid to improve tear film instability and ocular surface discomfort after cataract surgery. *Clin Ophthalmol*. 2019;13:1157–1163. doi:10.2147/OPTH.S208256
25. Wallerstein A, Jackson WB, Chambers J, Moezzi AM, Lin H, Simmons PA. Management of post-LASIK dry eye: a multicenter randomized comparison of a new multi-ingredient artificial tear to carboxymethylcellulose. *Clin Ophthalmol*. 2018;12:839–848. doi:10.2147/OPTH.S163744