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ORIGINAL RESEARCH

A Randomized Multicenter Study Comparing Low-Viscosity with Comparator 0.3% Hyaluronic Acid for the Treatment of Dry Eye Disease

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ABSTRACT

Introduction: To compare the efficacy and safety of a low-viscosity 0.3% hyaluronic acid (HA) ophthalmic solution with those of a comparator 0.3% HA formulation in patients with dry eye disease (DED).

Methods: In this double-blind, randomized, multicenter, noninferiority clinical trial, patients with mild-to-moderate DED were allocated at a 1:1 ratio to receive either low-viscosity or comparator 0.3% HA eye drops. Participants instilled the assigned study medications 5–6 times daily for 12 weeks, and a follow-up evaluation was conducted 1 week after the final instillation.

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The primary end point was the mean change in the corneal fluorescein staining (CFS) score from baseline to week 12. Secondary outcomes included the conjunctival staining score, tear break-up time (TBUT), nonanesthetized Schirmer test results, ocular surface disease index (OSDI) score, and ocular soreness.

Results: A total of 292 participants were included in the full analysis set. The change in CFS score at week 12 (–0.03; 95% CI –0.1873 to 0.1346) met the predefined noninferiority margin. Compared with the baseline parameters, both formulations significantly improved all ocular surface parameters except ocular soreness score (all $P<0.01$). No significant between-group differences were observed across all secondary outcomes. Notably, blurred vision immediately after instillation was significantly less frequent in the low-viscosity HA group at all time points ($P<0.01$).

Conclusions: Compared with the comparator 0.3% HA formulation, the low-viscosity 0.3% HA formulation demonstrated comparable therapeutic benefits while reducing the incidence of viscosity-related adverse events. These findings indicated that the low-viscosity 0.3% HA ophthalmic solution may serve as a clinically meaningful alternative for patients with mild-to-moderate DED.

Trial Registration: ClinicalTrials.gov identifier NCT06388070.

Keywords: HA ophthalmic solution; Corneal fluorescein staining; Dry eye disease; Hyaluronic acid

Key Summary Points

Why carry out this study?

Dry eye disease (DED) is a common, multifactorial disorder of the ocular surface that can impair visual function and reduce quality of life.

Hyaluronic acid (HA)-based artificial tears are a standard treatment for mild-to-moderate DED. While higher HA concentrations provide enhanced ocular surface protection, the resulting increase in viscosity often leads to transient blurred vision, which may reduce patient comfort and adherence.

This study compared the efficacy and safety of a low-viscosity 0.3% HA formulation with a comparator 0.3% HA formulation in patients with DED.

What was learned from the study?

In this study, the low-viscosity 0.3% HA formulation demonstrated noninferiority to the comparator 0.3% HA formulation in terms of efficacy over 12 weeks. Notably, the low-viscosity group exhibited a consistently lower incidence of postinstillation blurred vision across all time points.

These findings suggest that viscosity modulation is a critical strategy for maintaining therapeutic efficacy while minimizing viscosity-related visual disturbances in patients with mild-to-moderate DED.

INTRODUCTION

Dry eye disease (DED) is a common and multifactorial disorder of the ocular surface characterized by the loss of tear film homeostasis, ocular discomfort, and visual disturbance. The core pathophysiologic mechanisms include tear film instability, tear hyperosmolarity, inflammation, and epithelial barrier disruption, as defined in the TFOS DEWS III report [1]. DED is estimated to affect up to 50% of the population worldwide, and its prevalence continues to increase because of the aging of the population and increased daily exposure to digital devices [2, 3].

Clinically, patients with DED experience symptoms such as ocular discomfort, burning sensations, and fluctuations in vision, such as blurred or double vision, which can significantly interfere with daily activities, including reading, driving, professional work, and social

interactions, ultimately leading to a substantial reduction in quality of life [4, 5].

Artificial tears are commonly used for symptomatic management of mild-to-moderate DED and are frequently used as adjunctive therapy in more severe cases [6]. The primary therapeutic objective of artificial tears is to restore and maintain tear film stability, thereby alleviating symptoms, reducing visual fluctuations, and preventing ocular surface damage, particularly to the corneal epithelium [7].

Hyaluronic acid (HA)-based ophthalmic solutions are among the most widely prescribed lubricant formulations for DED [8]. HA is a naturally occurring glycosaminoglycan with strong hygroscopic and viscoelastic properties, which allow it to bind water molecules and adhere to the corneal epithelial surface. Through these mechanisms, HA promotes epithelial regeneration and improves the lubricating and protective functions of the natural tear film [9].

Commercially available HA formulations are produced in concentrations ranging from 0.1% to 0.3%. HA eye drops temporarily reduce viscosity, which facilitates their uniform spread across the ocular surface during blinking [10]. High-viscosity and relatively high-concentration HA formulations have been shown to prolong tear film retention time and improve tear film stability; however, they are also associated with transient adverse effects, most notably blurred vision following instillation [11, 12]. In particular, HA concentrations exceeding 0.2% have been shown to not only increase tear film stability but to also increase the incidence of patient-reported visual disturbances. Conversely, relatively low-viscosity HA formulations, while generally better tolerated, may reside on the ocular surface for shorter periods because of their diminished viscoelastic properties [11].

To address these limitations, a 0.3% HA ophthalmic formulation (Huons Co., Ltd., Gyeonggi-do, South Korea) was developed using patented rheological technology optimized for high-concentration HA. This low-viscosity platform employs HA polymers with precisely controlled molecular weight and reduced intrinsic viscosity, thereby minimizing intermolecular chain entanglement even at 0.3% concentration. As a result, it enhances ocular tolerability and visual comfort while maintaining therapeutic efficacy comparable to reference high-concentration HA formulations [13].

Although ophthalmic solutions at identical concentrations have been studied, direct comparisons of the efficacy and safety of HA eye drops with differing viscosities remain limited. To address this unmet need, a phase 3, randomized, active controlled clinical trial was conducted to evaluate the efficacy and safety of a low-viscosity 0.3% HA eye drop compared with an existing 0.3% HA formulation. The primary objective was to demonstrate noninferiority between the two treatments, as assessed by the change in corneal fluorescein staining (CFS) score from baseline to week 12 in the test group (low-viscosity HA 0.3%) and the control group (Hyalein Mini 0.3%).

METHODS

Study Design

This study was a prospective, multicenter, randomized, double-blind, active-controlled, noninferiority phase 3 clinical trial. The study consisted of a 2-week run-in period, a 12-week treatment period, and a 1-week follow-up period after the final treatment.

During the run-in period, all participants instilled carboxymethylcellulose sodium eye drops (High Eye Fresh Eye Drops 5 mg/mL, Huons Co., Ltd., Gyeonggi-do, South Korea) up to four times daily as needed. At the baseline visit, eligible participants who met all the inclusion criteria were randomized at a 1:1 ratio to either the test group or the control group. In this study, the test group received the investigational drug of low-viscosity 0.3% HA eye drops (4.7 cP), while the control group received comparator 0.3% HA eye drops of Hyalein Mini® (Santen, Osaka, Japan) developed by Santen Co., Ltd. (estimated 17 cP) [13, 14]. Participants in both groups were instructed to instill one drop in each eye 5–6 times daily throughout the treatment period (Fig. 1).

Randomization was performed using a stratified block randomization method based on the

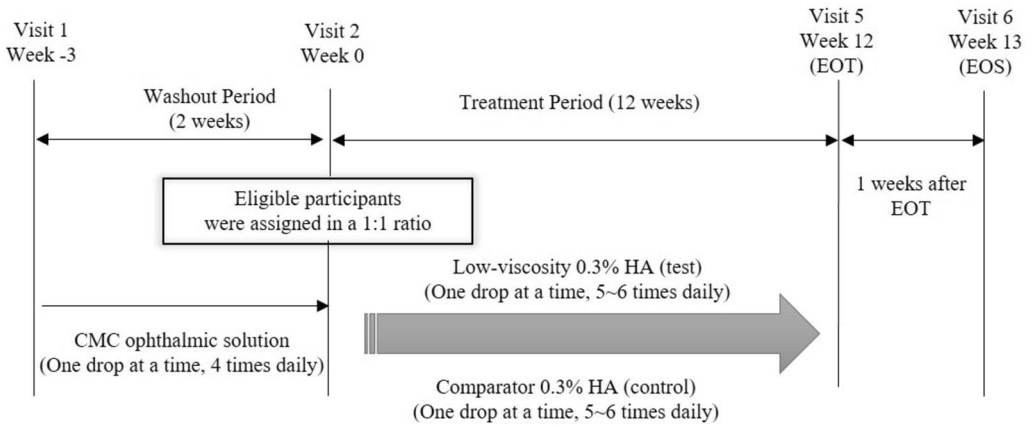

Fig. 1 Overview of the study design. *EOT* end of treatment, *EOS* end of study, *HA* hyaluronic acid, *CMC* carboxymethylcellulose

study site and baseline CFS score (Grade II or Grade III or higher). This study was conducted at Kangbuk Samsung Hospital (Coordinating Investigator site) and nine additional clinical research centers in South Korea, including Gyeongsan National University Hospital, Asan Medical Center, Korea University Anam Hospital, Pusan National University Hospital, Bucheon St. Mary's Hospital, Kangnam Sacred Heart Hospital, Kyungpook National University Hospital, Chosun University Hospital, and Severance Hospital, over an approximately 10-month study period. The trial was registered at ClinicalTrials.gov (NCT06388070) and was conducted in accordance with the principles of the Declaration of Helsinki and the CONSORT guidelines.

Participants

Eligible participants were adults aged 19 years or older who were diagnosed with DED at least 3 months prior to screening. Patients with grade II or higher DED, as defined by the diagnostic criteria of the Korean Corneal Disease Study Group, were eligible for inclusion.

Key inclusion criteria included a CFS score ≥ 2 based on the Oxford grading system, a tear break-up time (TBUT) ≤ 10 s, a nonanesthetized Schirmer test result ≤ 10 mm at 5 min, and an ocular surface disease index (OSDI) score ≥ 23 at screening [15].

Participants were excluded if they had undergone ocular surgery or experienced ocular trauma within 6 months prior to screening; had received treatment for meibomian gland dysfunction within 1 month prior to screening; had used soft contact lenses within 72 h before screening or during the study period; had ocular diseases, autoimmune diseases, or other systemic diseases; had an intraocular pressure (IOP) > 21 mmHg or a diagnosis of glaucoma at screening; or were pregnant, breastfeeding, or planning to become pregnant during the study period.

Efficacy and Safety Assessment

The primary end point was the change in the CFS score from baseline to week 12. Secondary end points included the change in CFS score from baseline to weeks 4 and 8; conjunctival staining score; nonanesthetized Schirmer test results; TBUT; OSDI score; and ocular soreness score according to a Numerical Rating Scale (NRS) at weeks 4, 8, and 12.

Corneal and conjunctival staining scores were assessed following the instillation of liquid sodium fluorescein and lissamine green dye, respectively, into the inferior conjunctival sac, followed by voluntary blinking. Staining scores for both the cornea and conjunctiva were graded according to the Oxford grading scheme and

ranged from 0 (absent) to V (severe) [16, 17]. TBUT was measured three times per eye after fluorescein liquid instillation, and the mean value was used for analysis. Safety assessments included the incidence of adverse events and comprehensive ophthalmic examinations, such as best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure measurement, and fundus examination. In addition, a questionnaire was administered throughout the study to assess postinstillation ocular symptoms, including blurred vision, foreign body sensation, ocular pain, ocular itching, soreness, dryness, and photophobia.

Statistical Analysis

All the statistical analyses were performed using monocular data from the eligible study eyes. The primary efficacy analysis evaluated the change in the CFS score from baseline to week 12 using an analysis of covariance (ANCOVA) model, with the baseline CFS score included as a covariate. Noninferiority analysis was conducted in the full analysis set (FAS). Noninferiority of the test group relative to the control group was assessed using the upper limit of the two-sided 95% confidence interval (CI) for the least-squares mean (LSMean) difference. Noninferiority was concluded if the upper limit of the CI was less than the predefined noninferiority margin of 0.289 [18].

Changes from baseline in the CFS score, conjunctival staining score, TBUT, nonanesthetized Schirmer test results, OSDI score, and ocular soreness score at each follow-up visit were analyzed using the paired *t* test or the Wilcoxon signed-rank test, as appropriate. The two-sample *t* test or the Wilcoxon rank-sum test was used for between-group comparisons. To provide 80% statistical power in demonstrating noninferiority using a one-sided two-sample *t* test with a significance level of 0.025 and an assumed standard deviation of 0.77, and accounting for an anticipated 20% dropout rate, the planned sample size was calculated as 280 participants. All the statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Study Participants

A total of 298 participants were randomized, and 297 participants received at least one dose of the study medication. The FAS included 292 participants (146 per group, test and control); five participants were excluded because of missing CFS data. Therefore, 141 participants in the test group and 142 participants in the control group completed the study (Fig. 2). The investigator assessed dosing compliance at each treatment visit (visits 3–5) after baseline (visit 2) by comparing the returned unused investigational products with the participant diary records. Compliance was evaluated for the period from the first administration of the investigational product at each visit until the day before the subsequent visit. For compliance assessment, the expected daily dosing frequency of the investigational product was defined as six instillations per day, and compliance was calculated on the basis of this six-times-daily regimen. During diary training for compliance monitoring, participants were encouraged to instill the eye drops six times daily whenever possible. Compliance was comparable between groups (test group: 96.48 ± 4.93%, range 81.94–109.26%; control group: 95.93 ± 5.19%, range 76.31–101.94%).

Baseline demographic and clinical characteristics were comparable between the two groups, with no statistically significant differences in sex, age, or duration of DED. At baseline, grade II DED was observed in 128 participants (87.07%) in the test group and 133 participants (88.08%) in the control group, whereas grade III DED was present in 19 participants (12.93%) and 18 participants (11.92%), respectively (Table 1).

Primary Efficacy Outcomes

The mean change in the average CFS score from baseline to week 12 (LSMean ± standard error) was −1.29 ± 0.06 in the test group and −1.27 ± 0.06 in the control group (Fig. 3). The test group was noninferior to the control group, as the upper limit of the two-sided 95%

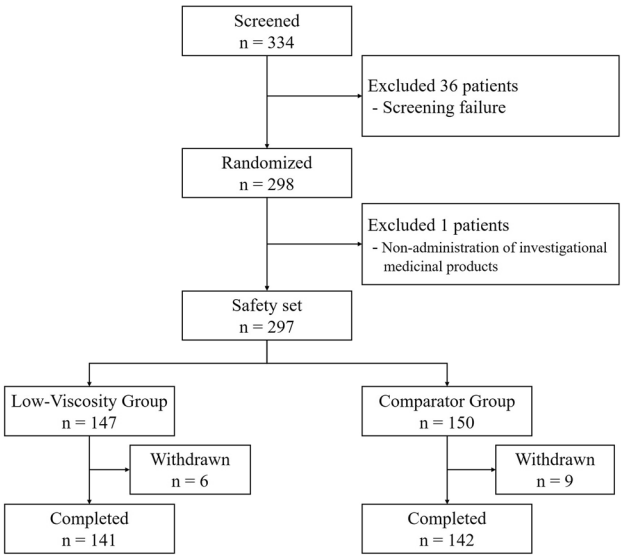

Fig. 2 Flow diagram of the study participants

Table 1 Baseline demographic and clinical characteristics of the study participants (randomized population)

Characteristic	Low-viscosity, *n* = 147	Comparator, *n* = 151	*P*-value
Age, year ± SD	43.66 ± 12.45	42.01 ± 12.45	0.2534[1]
Sex, *n* (%)			
Male	27 (18.37)	31 (20.53)	0.6374[2]
Female	120 (81.63)	120 (79.47)	
Duration of DED (month), mean ± SD	64.03 ± 58.92	57.59 ± 57.71	0.1338[1]
Baseline Grade II, *n* (%)	128 (87.07)	133 (88.08)	–
Baseline Grade III, *n* (%)	19 (12.93)	18 (11.92)	–

Low-viscosity low-viscosity 0.3% HA (test group), *Comparator* comparator viscosity 0.3% HA (control group), *DED* dry eye disease, *SD* standard deviation

[1]Wilcoxon rank-sum test, [2]chi-square test

confidence interval (CI) for the difference in the LSMean between the groups (95% CI, –0.1873 to 0.1346) was below the predefined noninferiority margin of 0.289.

Subgroup analyses based on baseline disease severity revealed that 127 participants in the test group and 130 participants in the control group had mild DED (Grade II), with a mean baseline CFS score of 2.00 in both groups. Moderate DED (Grade III) was present in 19 participants in the test group and 16 participants in the control group, with a mean baseline CFS score of 3.00 in both groups. In both severity subgroups, the CFS scores were significantly improved from the baseline score at all the study visits. However, no statistically significant differences were observed between the treatment groups at any time point (Tables 2 and 3; all $P > 0.05$).

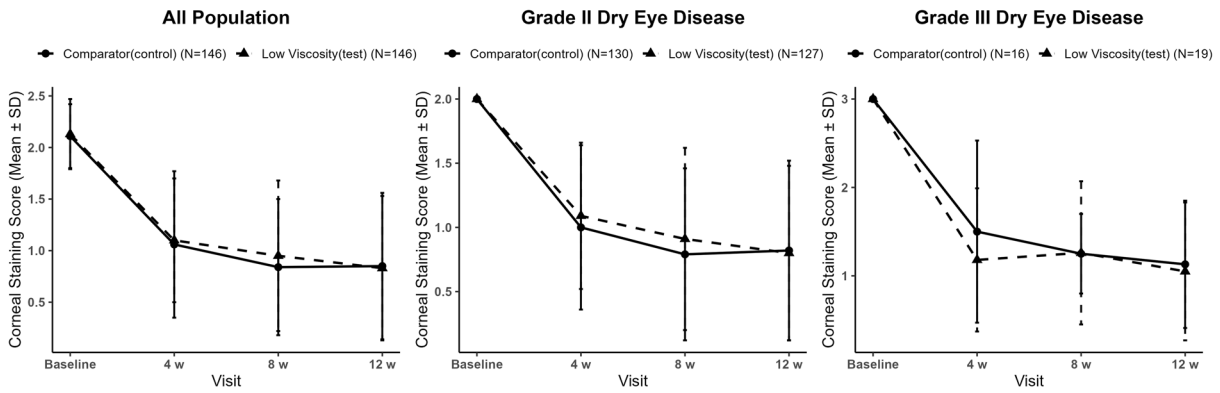

Fig. 3 Corneal fluorescein staining score from baseline to week 12

Table 2 Baseline corneal fluorescein staining (CFS) scores in participants with grade II dry eye disease

	Low-viscosity, $n = 127$ (Mean ± SD)	Comparator, $n = 130$ (Mean ± SD)	Group difference LSMean (95% CI)	*P*-value
Baseline	2.00 ± 0.00	2.00 ± 0.00		
4 week	1.09 ± 0.57	1.00 ± 0.64	0.09 (−0.06, 0.24)	0.2551
8 week	0.91 ± 0.71	0.79 ± 0.67	0.11 (−0.06, 0.28)	0.1876
12 week	0.80 ± 0.68	0.82 ± 0.70	−0.02 (−0.19, 0.15)	0.8161

Between-group comparisons were performed using analysis of covariance (ANCOVA); the baseline CFS score was used as a covariate

Low-viscosity low-viscosity 0.3% HA (test group), *Comparator* comparator viscosity 0.3% HA (control group), *CFS* corneal fluorescein staining, *CI* confidence interval, *LSMean* least-squares mean, *SD* standard deviation

Table 3 Baseline CFS scores in patients with grade III dry eye disease

	Low-viscosity, $n = 19$ (Mean ± SD)	Comparator, $n = 16$ (Mean ± SD)	Group difference LSMean (95% CI)	*P*-value
Baseline	3.00 ± 0.00	3.00 ± 0.00		
4 week	1.18 ± 0.81	1.50 ± 1.03	−0.32 (−0.98, 0.33)	0.3226
8 week	1.26 ± 0.81	1.25 ± 0.45	0.01 (−0.45, 0.47)	0.9540
12 week	1.05 ± 0.78	1.13 ± 0.72	−0.07 (−0.59, 0.45)	0.7787

Between-group comparisons were performed using ANCOVA; the baseline CFS score was used as a covariate

Low-viscosity low-viscosity 0.3% HA (test group), *Comparator* comparator viscosity 0.3% HA (control group), *CFS* corneal fluorescein staining, *CI* confidence interval, *LSMean* least-squares mean, *SD* standard deviation

Secondary Efficacy Outcomes

Secondary efficacy end points, including the conjunctival staining score, nonanesthetized Schirmer test results, TBUT, and OSDI score, significantly improved from baseline at all visits in both treatment groups (all $P<0.01$). However, no statistically significant differences between the test and control groups were observed for any secondary efficacy parameter at any study visit (Table 4; all $P>0.05$).

Safety Assessment

A total of 46 treatment-emergent adverse events (TEAEs) were reported in 34 of the 297 participants (11.45%) who received at least one dose of the investigational product (Table 5). The overall incidence of TEAEs did not differ significantly between the test and control groups.

Ocular adverse events were reported in 3 of 147 participants in the test group (2.04%; four events) and in 1 of 150 participants in the control group (0.67%; one event). Two adverse drug reactions (hordeolum) occurred in the control group, and all resolved during the study period. Separately, none of the ocular adverse events were considered related to the study medication. Study discontinuation owing to ocular adverse events occurred in one participant in the test group (macular hole) and one participant in the control group (retinal tear).

No clinically meaningful changes were observed in BCVA, slit-lamp biomicroscopy findings, intraocular pressure, or fundus examination results throughout the study.

Ocular Symptom Assessment

Postinstillation ocular symptom assessments revealed that the incidence of blurred vision was significantly lower in the test group than in the control group on day 1 and at weeks 4, 8, and 12 (all $P<0.01$; Fig. 4).

DISCUSSION

This study represents the first phase 3 randomized clinical trial to evaluate the efficacy and safety of a low-viscosity ophthalmic solution containing 0.3% HA. An investigational drug was developed to mitigate postinstillation discomfort, particularly transient blurred vision, which is commonly associated with comparator high-viscosity HA formulations. Following regulatory approval by the Ministry of Food and Drug Safety (MFDS) in 2023 as for clinical trial, the present trial provides clinical evidence supporting the therapeutic value and tolerability of this formulation.

HA is a natural polymer with excellent biocompatibility and biodegradability, and its rheological properties play a critical role in ocular

Table 4 Changes in secondary efficacy variables at week 12

Measure	Change from baseline (LSMean ± SE)		Group difference LSMean (95% CI)	*P*-value
	Low-viscosity	Comparator		
Conjunctival staining score	−1.05 ± 0.10	−1.03 ± 0.10	−0.02 (−0.23, 0.19)	0.8774
Nonanesthetized Schirmer test (mm)	2.60 ± 0.59	2.80 ± 0.61	−0.20 (−1.47, 1.07)	0.7567
TBUT (s)	1.63 ± 0.18	1.61 ± 0.18	0.02 (−0.36, 0.40)	0.9245
OSDI score	−27.44 ± 1.79	−25.71 ± 1.83	−1.74 (−5.62, 2.15)	0.3795

Between-group comparisons were performed using ANCOVA; the baseline CFS score and grade were used as covariates

Low-viscosity low-viscosity 0.3% HA (test group), *Comparator* comparator viscosity 0.3% HA (control group), *CI* confidence interval, *LSMean* least-squares mean, *OSDI* ocular surface disease index, *SE* standard error, *TBUT* tear break-up time

Table 5 Treatment-emergent adverse events during the study period

Ocular and nonocular adverse events[a]	**Low-viscosity, *n* = 147** ***n*** **(%)**	**Comparator, *n* = 151** ***n*** **(%)**
No. of TEAEs	20	26
Participants with at least one TEAE	14 (9.52)	20 (13.33)
Participants discontinued treatment due to an adverse event	1 (0.68%)	1 (0.67%)
Ocular adverse events		
No. of TEAEs	4	1
Participants with at least one ocular adverse event	3 (2.04)	1 (0.67)
Conjunctival hyperemia	1 (0.68)	–
Conjunctival edema	1 (0.68)	–
Diplopia	1 (0.68)	–
Macular hole	1 (0.68)	–
Retinal tear	–	1 (0.67)

Low-viscosity low-viscosity 0.3% HA (test group), *Comparator* comparator viscosity 0.3% HA (control group), *TEAE* treatment-emergent adverse event

[a]MedDRA (28.0)

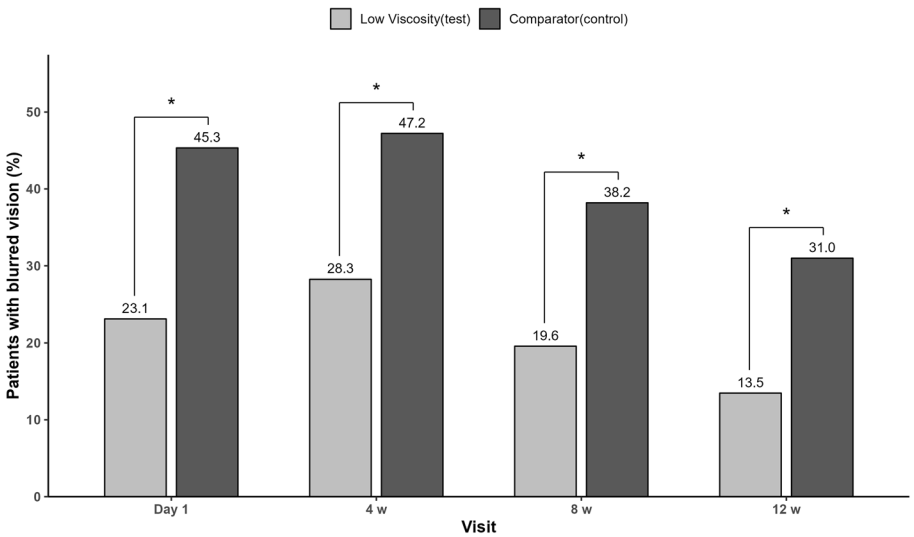

Fig. 4 Incidence of blurred vision during the study period. Between-group comparisons were performed using chi-square tests at each time point (*$p < 0.01$)

surface retention and drug bioavailability. In particular, the shear-thinning behavior of HA allows a temporary reduction in viscosity during blinking, facilitating uniform distribution and enhanced interaction with the ocular surface [9, 10, 19–21]. While increased viscosity can improve tear film retention, excessive viscosity may result in transient visual disturbance after instillation, making patient comfort and adherence important considerations in the long-term management of DED.

In general, increasing the viscosity of ophthalmic solutions prolongs precorneal residence time by reducing tear clearance, thereby increasing bioavailability [11]. Previous studies have suggested that the optimal viscosity range for therapeutic efficacy lies between 15 and 30 cP [22]. Notably, despite having a lower viscosity (4.7 cP), the investigational formulation induced significant improvements over 12 weeks in multiple objective and subjective end points, including CFS, conjunctival staining, the non-anesthetized Schirmer test results, TBUT, and OSDI scores. Importantly, noninferiority to the comparator 0.3% HA formulation with standard viscosity was confirmed for the primary end point. Stratified analyses based on disease severity revealed consistent treatment effects across severity subgroups, suggesting that the low-viscosity formulation may be applicable not only to patients with mild DED but also to those with moderate disease.

From a safety and tolerability perspective, the low-viscosity HA formulation was well-tolerated, with no major adverse events or drug-related safety concerns identified. No participants reported severe postinstillation blurred vision, and the incidence of blurred vision was significantly lower in the test group than in the control group at all the study visits. In a prospective crossover trial evaluating 0.1% HA and low-viscosity 0.3% HA formulations, both concentrations improved ocular surface parameters, and importantly, no significant differences were observed in patient-reported symptoms such as blurred vision or instillation discomfort [23]. These findings indicate that the viscosity profile of HA may play a more decisive role in determining postinstillation comfort than the HA concentration itself does. Furthermore, the viscosity profile of the high-concentration HA formulations prolongs ocular surface residence and maintains an instillation comfort profile comparable to that of low-concentration HA formulations. These findings are clinically relevant, as postinstillation visual disturbance is a known factor that can negatively affect patient satisfaction and treatment adherence. In contrast to antiinflammatory agents such as topical cyclosporine, which are frequently associated with burning or stinging sensations upon instillation and may limit compliance, the low-viscosity HA formulation demonstrated favorable tolerability in patients with mild-to-moderate DED [24].

Several previous studies have reported that 0.3% HA eye drops provide therapeutic benefits comparable to those of topical cyclosporine. In the present study, the mean reduction in the CFS score exceeded one point at 12 weeks, which is greater than the approximately 0.6–0.7 point reduction reported in phase 3 cyclosporine trials. However, direct comparisons should be interpreted with caution, as studies on cyclosporine generally included patients with moderate-to-severe DED (baseline CFS scores of approximately 2.61–2.77), whereas the present study primarily included patients with mild-to-moderate disease (baseline CFS scores of approximately 2.11–2.13). Accordingly, definitive conclusions regarding superiority over cyclosporine cannot be drawn [25]. Similarly, a study by Park et al. reported comparable reductions in CFS scores between 0.3% HA and 0.05% cyclosporine after 12 weeks of treatment. Nonetheless, differences in study design, inclusion criteria, and baseline disease severity limit the validity of direct cross-trial comparisons, underscoring the need for cautious interpretation [26].

Artificial tears are generally recommended as first-line therapy for mild-to-moderate DED and are frequently used in combination with anti-inflammatory or immunomodulatory agents in more severe cases [27]. The present trial was designed to evaluate the efficacy of 0.3% HA monotherapy, and the use of concomitant ophthalmic medications was prohibited. Consequently, the enrollment of patients with moderate-to-severe DED requiring combination therapy was limited, with the majority of participants classified as having mild disease. This

limited the ability to fully assess epithelial healing and symptom improvement with HA monotherapy in patients with advanced-stage disease. In addition, the relatively small proportion of patients with grade III or higher DED reduced the statistical power of the subgroup analyses, and the 12-week follow-up period may be insufficient for evaluating long-term safety and sustained efficacy.

Future studies with longer follow-up durations, larger sample sizes, and broader inclusion of patients across the full spectrum of DED severity are warranted to further elucidate the clinical implications of viscosity-modulated HA formulations and to better define their role in long-term DED management.

Limitations

This study has several limitations. Most participants administered the eye drops six times daily, subgroup analysis comparing the five-times-daily and six-times-daily dosing groups was not conducted. Although we assessed the incidence and severity of transient blurred vision and ocular discomfort immediately after instillation—symptoms commonly associated with higher-viscosity formulations—we did not directly measure dynamic viscosity under physiologic shear conditions or evaluate objective ocular surface residence time. Therefore, mechanistic interpretations regarding the relationship between viscosity and visual disturbance should be made cautiously. In addition, while 0.3% HA formulations are generally associated with greater transient visual disturbance than lower-concentration formulations due to increased tear film thickness and optical irregularity [28], our study did not include detailed assessments of functional visual performance or occupation-specific visual demands. Consequently, the practical impact of reduced postinstillation blur on work-related activities or visually demanding tasks could not be fully determined. Furthermore, the study population predominantly consisted of patients with mild-to-moderate DED, and the follow-up period was limited to 12 weeks. These factors may have contributed to the absence of significant between-group differences in patient-reported outcomes such as OSDI scores. Future studies incorporating objective rheological measurements, functional vision assessments, and more diverse patient populations—including individuals engaged in visually intensive occupations—are warranted to better define the clinical implications of viscosity modulation in high-concentration HA formulations.

CONCLUSIONS

In this phase 3 randomized clinical trial, the therapeutic efficacy of low-viscosity 0.3% HA eye drops was noninferior to that of a comparator 0.3% HA formulation in patients with mild-to-moderate dry eye disease. Notably, the low-viscosity formulation was associated with a lower incidence of viscosity-related visual disturbance, indicating improved tolerability. These findings suggest that a low-viscosity 0.3% HA eye drop may represent an effective and well-tolerated therapeutic option for the management of dry eye disease.

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Data Availability. Data are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Seong Jae Kim, Jae Yong Kim, Dong Hyun Kim, Jong Soo Lee, Eun Chul Kim, Young Ju Shin, Hong Kyun Kim, Jae Woong Koh, Tae-im Kim, Da Hye Jung, and Chul Young Choi have nothing to disclose.

Ethical Approval. This study adhered to the tenets of the Declaration of Helsinki and the guidelines of Good Clinical Practice and was approved by the Institutional Review Board at Kangbuk Samsung Hospital; Approval No. KBSMC 2023-11-020. The study was approved by all participating ethics committees(Kangnam Sacred Heart Hospital; Approval No. HKS IRB 2023-11-013, Kyungpook National University Hospital; Approval No. HNUH 2023-11-016, Gyeongsang National University Hospital; Approval No. GNUH 2023-11-017, Korea University Anam Hospital; Approval No. 2024AN0035, Pusan National University Hospital; Approval No. 2312-001-144, Catholic University Bucheon St. Mary's Hospital; Approval No. HC23M-DDT0118, Asan Medical Center; Approval No. 2023-1556, Yonsei University Severance Hospital; Approval No. 4-2024-0025, and Chosun University Hospital; Approval No. CHOSUN 2023-11-008) and all patients provided written informed consent before study screening.

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