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Corneal Staining Responder Analysis

A Clinically Meaningful Dry Eye Outcome

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Purpose: Thus far, clinical studies related to dry eye disease (DED) have focused on demonstrating a statistically significant difference in various ocular surface and tear film parameters and patient symptoms between the test arm versus comparator. However, it is largely unclear what arm differences or magnitude of improvement for a given parameter are clinically meaningful. This study aims to assess the correlations between corneal punctate erosions and patient-reported symptoms and aims to define "corneal staining responder" as a physician-measured and clinically meaningful DED outcome to be used in clinical studies and patient care.

Design: Retrospective analysis of previously published studies.

Participants: A total of 1704 adult patients with evaporative or aqueous deficient DED who participated in 4 large-scale randomized, controlled studies evaluating 2 different DED medications (a water-free cyclosporine 0.1% solution and perfluorohexyloctane ophthalmic solution) or their respective comparators (vehicle and saline solution).

Methods: Corneal punctate epithelial erosions were evaluated using fluorescein dye, and the staining score was graded according to the National Eye Institute scale (0–15). "Corneal staining responder" was defined as a $\geq$3 grade improvement from baseline, based on published literature and expert opinion. A variety of patient symptoms were assessed using a visual analogue scale (0–100).

Main Outcome Measure: Corneal staining responders were compared with nonresponders regarding improvement in symptoms via analysis of covariance irrespective of the treatment received.

Results: In all 4 studies, corneal staining responders showed numerically greater improvement in all assessed DED symptoms compared with nonresponders. Overall, 36 comparisons were performed involving 14 different DED symptoms. In 75% of the comparisons, the magnitude of the symptom improvement in responders was statistically significantly greater compared with nonresponders. This finding was consistent across all 4 studies, irrespective of the treatment applied, the patient demographics, and the severity or type of DED.

Conclusions: This analysis demonstrates that a $\geq$3 severity grade improvement in corneal staining score is consistently associated with significant corresponding symptom improvement and may represent a clinically meaningful DED outcome measure for clinical studies and patient care.

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See Commentary on page 1342.

Dry eye disease (DED) is highly prevalent in the adult population globally and has a significant impact on quality of life due to discomfort symptoms and impaired visual function.[1] In line with the multifactorial nature of the disease, its clinical presentation is heterogenous. According to the international Tear Film and Ocular Surface Society Dry Eye Workshop II, the diagnosis requires a combination of physician-measured clinical signs (e.g., ocular surface staining, tear break-up time, and tear film osmolarity) and patient-reported symptoms (e.g., eye discomfort, eye pain, blurred/fluctuating vision).[2] However, there is no single agreed upon outcome measure or standardized metric to diagnose or follow the disease's process. The lack of correlation among the various ocular surface and tear film parameters and the well-known discordance between patient-reported symptoms and physician-measured signs[3,4] thus far have hampered the development of new treatment avenues and impacted patient care in the clinical setting. The US Food and Drug Administration draft guidance "Dry Eye: Developing Drugs for Treatment; Guidance for Industry" does not require any specific signs to be chosen. Also, there is no requirement that signs and symptoms are demonstrated in the same study or DED population, and it allows only statistically significant differences between the treatment arm and its comparator.[5,6] It remains unknown if such an improvement is clinically meaningful. In addition, there is a lack of uniformity regarding which parameter(s) shall be monitored in clinical practice to assess treatment efficacy on initiation of the approved treatment.[4]

Corneal fluorescein staining is the most frequently performed DED diagnostic test in clinical care.[2] The vital dye-stained areas of the corneal epithelium represent punctate

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erosions and have a high impact on visual function due to light scatter causing higher-order aberrations and decreased contrast sensitivity.[7] There is growing evidence regarding its relationship to visual function and vision-related quality of life outcomes.[8-12] Arguably, the most common visual symptom reported by patients with DED is difficulty with reading. Previous studies demonstrated a direct inverse correlation between corneal staining score and reading speed.[13-15] In fact, corneal staining score has been proposed as the primary objective outcome measure to assess the efficacy of DED treatments.[12] The recently published consensus guidance from a group of European DED experts also highlights the importance of corneal staining in determining the severity of the disease.[16]

We aim to study the magnitude of improvement in corneal staining score that has a measurable impact on patient-reported symptoms to propose its validity as a clinically meaningful DED outcome measure.

Methods

Data from 4 large-scale, randomized, double-masked clinical studies involving 2 topical DED treatments with different modes of action and different study populations were analyzed retrospectively.

The studies, as summarized in Table 1, comprised 1 phase 2 study (Study #1 [SEECASE]) including patients with mild to moderate evaporative DED[17] and 3 phase 3 studies (Study #2 [ESSENCE 1], Study #3 [ESSENCE 2], and Study #4 [SHR 8028-301]) including patients with moderate to severe aqueous deficient DED.[18-20] The full methodology for each of the included studies can be found in the respective primary publications.[17-20] Institutional Review Board/Ethics Committee approval was obtained for all studies, and participants provided written informed consent before study enrollment. These studies were conducted in accordance with International Council on Harmonisation of Good Clinical Practice and the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Efficacy Outcome Measures

In all 4 studies, corneal epithelial staining, evaluated using the National Eye Institute (NEI) grading scale (0−15), was the primary sign end point. Briefly, the epithelium is evaluated in 5 sections (superior, inferior, nasal, temporal, and central) with each section graded between 0 and 3 according to the number/density of the erosions assessed visually.[21] The system is not a linear scale; there is an exponential increase in the number of stained dots with grades. Thus, a decrease of 1 severity grade in a given region typically corresponds to a 3-fold reduction in the number of punctate erosions. The difference in the number of punctate lesions between grades is even larger in regions with severe and confluent staining.[22]

A responder analysis is a useful approach to demonstrate that the observed differences in the primary end point are not only statistically significant but also clinically meaningful.[23] For the purpose of this study, "corneal staining responder" was tentatively defined as a decrease of ≥3 grades (0−15) from baseline based largely on published articles as well as guidance from queried key opinion leaders who considered this level as meaningful improvement reflecting the healing of the ocular surface.[24,25]

Schirmer's test without anesthesia was also assessed in all studies to determine tear production as another DED outcome measure. An increase of 10 mm or more from baseline was defined as "Schirmer's test responder."[6]

Symptoms of DED were assessed using the Visual Analogue Scale, a patient-reported index, ranging from 0 for no symptom to 100 maximal symptom severity. In Study #1 and Study #2, the following 10 symptoms were assessed: severity of dryness, frequency of dryness, blurred vision, awareness of eyes, burning/stinging, foreign body sensation, itching, sensitivity to light, pain, and sticky feeling. In Study #3 and Study #4, the following 8 symptoms were assessed: severity of dryness, frequency of dryness, blurred vision, awareness of eyes, difficulty reading, fluctuating vision, looking at screens, and driving at night.

Statistical Analysis

In all studies, the "corneal staining responder" rates in the active arm were compared with the comparator arm at the primary end point visit. This was the prespecified analysis in all but 1 study (Study #2), where the analysis was conducted post hoc. The comparison was performed via the Fisher test in Study #1 and Study #2, whereas Study #3 and Study #4 used a logistic regression. Similar comparisons between treatment arms were performed for Schirmer's test responder analyses.

The unit of comparison was the change from baseline in the assessed parameter (corneal staining score, Schirmer's tear test score, and patient-reported symptoms) measured at the primary end point visit in each study.

To assess the correlations between corneal punctate erosions and patient-reported symptoms, change from baseline in a variety of symptoms was compared between "corneal staining responders" and "nonresponders" in each of the 4 studies. The comparison was made irrespective of treatment via an analysis of covariance model that includes baseline value and responder arm. Data were not pooled across studies. In a sensitivity analysis, additional comparisons were performed using a modified definition of corneal staining responder, an improvement in total corneal staining ≥2 severity grades, and Schirmer's test responder.

All analyses were based on the Full Analysis Set population (all participants who received ≥1 dose of investigational product). All *P* values reported are nominal and not adjusted for multiplicity.

Results

Characteristics of the Studies

A summary of the study characteristics is provided in Table 1. The 4 studies included a total of 1704 patients with DED. Across the 4 different studies, there were differences in the geographic regions, patient demographics (age and race/ethnicity), subtype and severity of the DED studied, and treatments used.

Three studies were conducted in the United States, and 1 study took place in China. The active treatments were perfluorohexyloctane ophthalmic solution and a water-free cyclosporine 0.1% solution; the comparators consisted of 0.9% saline solution and the water-free vehicle, respectively.

Demographics of participants and their baseline DED findings are summarized in Table 2. In all 4 studies, patients had to have a certain minimum corneal epithelial damage (measured as corneal punctate erosions) as well as

Table 1. Overview of Four Large-Scale Dry Eye Disease Treatment Studies Analyzed in This Trial

	Study #1 SEECASE (NVU-002) Tauber 2021[17]	Study #2 ESSENCE-1 (CYS-003) Sheppard 2021[18]	Study #3 ESSENCE-2 (CYS-004) Akpek 2023[19]	Study #4 SHR 8028-301 Peng 2024[20]
Phase	2	2b/3	3	3
Clinical Trial ID	NCT03333057	NCT03292809	NCT04523129	NCT05841043
Population	Evaporative	Aqueous deficient	Aqueous deficient	Aqueous deficient
Country	United States	United States	United States	China
No. Patients Verum/ Comparator	114/111/111	162/166	423/411	103/103
Duration (Days)*	57	29	29	29
Treatment	Perfluorohexyloctane	Cyclosporine 0.1%	Cyclosporine 0.1%	Cyclosporine 0.1%
Key Inclusion Criteria	tCFS 4 ≤X ≤ 11 (NEI), OSDI ≥25, TFBUT ≤5 sec, Schirmer's ≥5 mm, MGD score ≥3	tCFS ≥10 (NEI), OSDI ≥20, Schirmer's 1 ≤X ≤10 mm	tCFS ≥10 (NEI), dryness score ≥50, Schirmer's 1 ≤X ≤10 mm	

MGD = meibomian gland dysfunction; NEI = National Eye Institute; OSDI = Ocular Surface Index; tCFS = total corneal fluorescein staining; TFBUT = tear film break-up time.
*For primary end point assessment for study #1 verum QID/Verum BID/comparator.

presence of patient-reported symptoms required by inclusion/exclusion criteria as per the study protocol.

The population in Study #1 had predominantly evaporative DED as indicated by normal Schirmer's scores and presence of meibomian gland dysfunction. Studies #2 to #4 were characterized by low Schirmer's scores (3.8 to 5.2 mm/5 min), indicative of a predominantly aqueous deficient DED population.

Responder Rates in Active versus Comparator Arms

The corneal staining and Schirmer's test responders are summarized in Table 2. In all 4 studies, the corneal fluorescein staining responder rate was statistically significantly higher in the active arm compared with the comparator arm at the primary end point visit. In Study #1, the corneal staining responder rates were 40.4% in the perfluorohexyloctane arm versus 26.1% in the saline arm at day 57. In Studies #2, #3, and #4, the corneal staining responder rates were 52.9%, 71.6%, and 77.8%, respectively, in the cyclosporine 0.1% arm versus 40.6%, 59.7%, and 47.1%, respectively, in the comparator arm at day 29.

The Schirmer's responder rates at 4 or 8 weeks of treatment were low and typically in the single-digit range across all 4 studies. The difference between the active and the comparator arm was significant in Study #3 (11% vs. 7%). Of note, Study #1 included patients with normal Schirmer's tear test scores at baseline; therefore, in those patients it may be difficult to increase this value by another 10 mm/5 min. Studies #2 to #4 included patients who had on average very low Schirmer's tear test scores, which also presents a hurdle to see increases of ≥10 mm increase within 4 weeks of treatment.

Table 2. Overview of Main Demographics and Baseline Characteristics of Patients in Four Large-Scale Dry Eye Treatment Studies Analyzed in This Trial

	Study #1 SEECASE (NVU-002) Tauber 2021[17]	Study #2 ESSENCE-1 (CYS-003) Sheppard 2021[18]	Study #3 ESSENCE-2 (CYS-004) Akpek 2023[19]	Study #4 SHR 8028-301 Peng 2024[20]
Mean Age (yrs)	53.6 (16.22)	61.4 (13.11)	57.1 (15.83)	47.8 (14.24)
Female (%)	72.3%	71.6%	73.0%	89.8%
Duration of Dry Eye (yrs*)	8.5 (6.73)	12.3 (10.63)	10.4 (9.93)	4.6 (4.74)
Corneal Staining	6.8 (2.07)	11.5 (1.25)	11.5 (1.38)	12.2 (1.84)
Staining Responder (%)*	40/35/26	53/41	72/60	78/47
Schirmer's Test (mm/5 min)	14.6 (8.96)	5.2 (2.73)	4.9 (2.87)	3.8 (2.54)
Schirmer's* Responder (%)	7/4/3	5/4	11/7	8/7
TBUT (s)	2.97 (0.91)	2.31 (0.94)	3.32 (1.51)	2.36 (1.12)
Dryness (VAS 0–100)	68.47 (21.06)	69.2 (21.03)	70.2 (12.56)	73.0 (12.75)
Blurred Vision (VAS 0–100)	54.34 (28.44)	51.1 (28.97)	52.7 (25.79)	49.8 (25.90)

TBUT = tear break-up time; VAS = Visual Analogue Scale.
Data are reported as average and ± standard deviation and percentage of population gender and responder.
*The percentage of responders in verum/comparator (for Study #1 verum QID/Verum BID/comparator).

Symptom Improvement in Responders versus Nonresponders

Figure 1 depicts the change in symptoms in corneal staining responders versus nonresponders. In all 4 studies, corneal staining responders showed numerically greater improvement in *all* measured DED symptoms compared with nonresponders. These improvements reached statistical significance over nonresponders in 27 of 36 comparisons (75%). In Study #3, the largest study, corneal staining responder analysis on symptoms was performed for each treatment arm separately (data not shown). Within each treatment arm, the responders experienced a more pronounced improvement for all assessed symptoms. The average difference across studies between responders and nonresponders in those Visual Analogue Scale symptoms

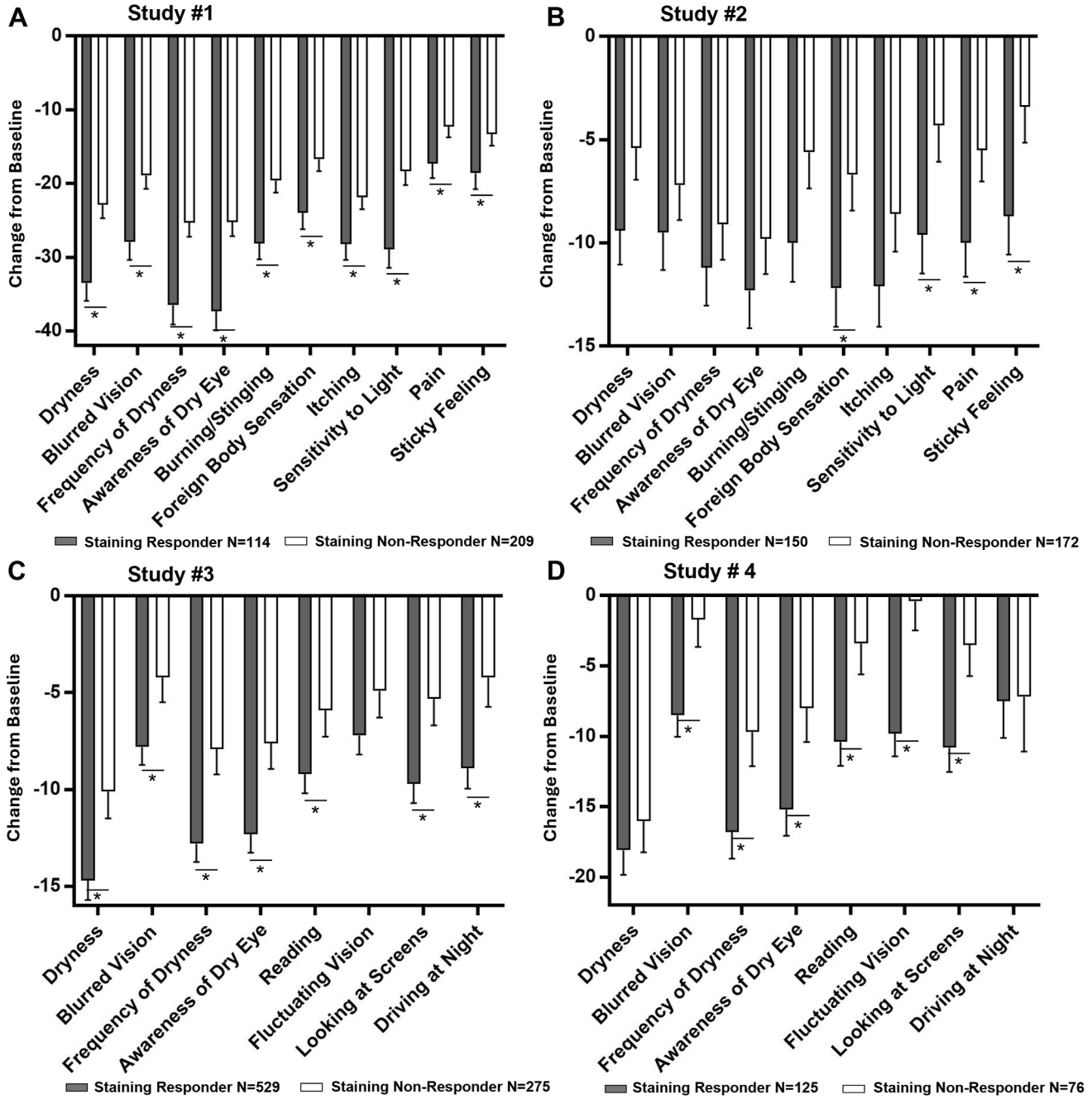

Figure 1. Mean change from baseline in a variety of dry eye symptoms assessed using the visual analogue scale (0 for no symptom to 100 maximal symptom severity) in corneal staining responders versus nonresponders at the primary end point visit of each study: **A,** Study #1; **B,** Study #2; **C,** Study #3; and **D,** Study #4. *$P \leq .05$.

assessed in all 4 studies (severity of dryness, frequency of dryness, blurred vision, awareness of eyes) was approximately 5 units.

A sensitivity analysis compared patients with ≥2 severity grades improvement in the corneal staining score with those without such a response. Those patients with ≥2 grades improvement in total corneal fluorescein staining also showed numerically larger corresponding symptom improvements compared with nonresponders. The difference reached statistical significance in 15 of the 36 comparisons (41%). In the largest study, Study #3, the patients with ≥2 severity grades improvement in corneal staining score did not have a statistically significant symptom score improvement in any of the measured symptoms. This sensitivity analysis suggests that an improvement of ≥2 severity grades in corneal staining score is not large enough to consistently result in measurable impact in symptomatology.

An increase in Schirmer's test score ≥10 mm is a US Food and Drug Administration–accepted DED end point for studies. Therefore, we repeated similar symptom analyses in Schirmer's responders versus nonresponders in the same 4 studies. In 20 unique comparisons, Schirmer's responders showed numerically larger improvements on symptoms compared with nonresponders. However, in 16 other comparisons, the nonresponders showed a numerically larger or same improvement in symptoms compared with the responders. None of the differences were statistically significant.

Discussion

Corneal staining using fluorescein dye is the most frequently performed clinical test in eyecare practice to diagnose and manage DED.[26] The areas of the corneal epithelium that take up the dye, observed as punctate staining, are believed to be drop-off of cells due to inflammation and desiccation. Irregularities of the corneal epithelium have a significant impact on image quality, largely due to reduced contrast sensitivity and higher-order aberrations.[9-11] Thus, patients with DED commonly experience blurred or fluctuating vision, particularly with activities that require sustained gazing such as reading or driving.[13-15] Punctate epithelial erosions also are associated with ocular discomfort.[26] Indeed, corneal staining is a commonly used DED sign end point in clinical studies. However, the studies showing the most appropriate grading scale to be used or the magnitude of clinically meaningful change are lacking.

An improvement in corneal staining of ≥3 grades using the nonlinear NEI scale is considered clinically meaningful by experts as published in the literature.[18-20] Our analysis across 4 independent, large clinical studies showed that in corneal staining responders, there was a consistent corresponding improvement in patient-reported symptoms compared with nonresponders for all symptoms investigated, suggesting that this level of improvement is also relevant for the patients. The evidence for this correlation is compelling. In 75% of the 36 tests, we found a statistically significant symptom improvement in corneal staining responders. The magnitude of difference (~5 units) between responder and nonresponder for measures of dryness/ocular discomfort is in the same range as seen for previously Food and Drug Administration–approved products compared with their vehicles, suggesting that the level of difference is meaningful.[27,28] Of note, the analyses included patients with different DED subtypes and severity, and studies tested different treatments and were conducted in different geographical regions, yet all showed a consistent pattern of better symptom improvements in corneal fluorescein staining responders. This suggests that the observed association between an improvement in corneal staining score ≥3 grades and symptom improvement seem to be generalizable. A smaller improvement in corneal fluorescein staining, ≥2 grades, on the other hand, was not associated with such a consistent effect on symptomatology, supporting that our tentative threshold definition of ≥3 severity grades is a clinically relevant response. In addition, our study did not show such correlations in Schirmer's responders.

These findings are in contrast to earlier publications noting that the association between physician-measured DED signs and patient-reported symptoms is weak and inconsistent.[4] Of note, this analysis included only studies that enrolled patients who presented with corneal staining and symptoms. Another important distinction is that instead of correlating absolute values at certain timepoints, the magnitude of change from baseline was investigated in this study. This way, each patient had 2 separate measurements of each parameter, thereby serving as internal control and potentially allowing for more accurate correlation.

Of note, in case of weak correlations, the effect size needs to be sufficiently large to detect the association between signs and symptoms. That means that not only the responder criterion needs to be meaningful but also the proportion of patients fulfilling the criterion needs to be meaningful. All 4 studies showed strong treatment responses in corneal staining with average changes from baseline ranging from −1.8 in Study #1 up to −4.8 in Study #4 and response rates ranging from 35.1% to 77.8%, respectively. Compared with the literature regarding other approved DED treatments,[29-31] the treatment response was higher, potentially allowing to better detect the associations seen here. On the other hand, the lower percentage of Schirmer's responders could explain why we did not find the correlations for Schirmer's responders with symptoms.

The results reported in this article are in line with observations that corneal staining has a measurable impact on vision-related function. In Study #2, corneal staining responders showed a significantly higher and clinically meaningful (>10 words/min) improvement in reading speed compared with nonresponders.[18,32] The results of other publications also showed that a difference of ≥3 grades in the corneal punctate erosions is associated with an approximately 10 words per minute difference in reading speed.[13-15,33] This further supports that an improvement of ≥3 scores in the corneal punctate erosions score represents a meaningful threshold.

Limitations

Our study is not without limitations. The main limitation of this study is the post hoc nature of the analyses and thus formally exploratory in nature. Another limitation is the exclusion of participants with very mild corneal staining ($\leq$4), which may preclude the generalizability of the results. However, it is well known that individuals without significant corneal punctate erosions, referred to as "pain without stain," may not necessarily have DED.[34]

Conclusions

Our analysis demonstrates that an improvement in corneal staining score $\geq$3 grades (using the NEI scale) is associated with significant corresponding DED symptom improvement and therefore may represent a meaningful physician-measured end point for clinical studies and patient care independent of the nature of the disease or treatment used.

Footnotes and Disclosures

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No animal subjects were used in this study.

AUTHOR CONTRIBUTIONS

Conception and design: Akpek, Sheppard, Krösser

Data collection: Sheppard, Krösser

Analysis and interpretation: Akpek, Krösser

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Abbreviations and Acronyms:
DED = dry eye disease; **NEI** = National Eye Institute.

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