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Lacripep for the Treatment of Primary Sjögren's–Associated Ocular Surface Disease: Results of the First-In-Human Study

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Purpose: The purpose of this study was to assess the safety, tolerability, dosing, and efficacy of the active 19 amino acid fragment of lacritin (Lacripep), a broad regulator of ocular surface homeostasis, in the treatment of ocular surface disease associated with primary Sjögren's syndrome.

Methods: Two hundred four subjects were randomized to receive vehicle, 22 μM Lacripep, or 44 μM Lacripep 3 times daily for 28 days, preceded by a 14-day run-in and followed by 14-day washout. Outcome measures were corneal fluorescein staining (CFS), lissamine conjunctival staining, Schirmer with anesthesia, tear break-up time, SANDE scoring, and visual analog scale assessment of symptoms.

Results: This study established the safety and tolerability of topical treatment with Lacripep in patients with primary Sjögren's syndrome. There were few adverse events: Only mild irritation was found in less than 3 percent of patients dosed with Lacripep. Total CFS and Eye Dryness Score were not significantly changed at day 28. Post hoc analysis of patients with Eye Dryness Severity scores of 60 or greater at baseline revealed significant improvements in inferior CFS at 14 and 28 days and complaints of burning and stinging at 14 days. Significant improvement in regional lissamine conjunctival staining was seen at 14 and 28 days.

Conclusions: This first-in-human study of Lacripep in patients with primary Sjögren's syndrome demonstrated clinically significant improvements in specific signs and symptoms on which to base future studies. This study established safety and tolerability and potential metrics of efficacy in patients with moderate to severe disease. Further work on appropriate dosing and concentration is ongoing.

Key Words: dry eye, lacritin, Sjögren's disease

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The primary objective of this study was to evaluate the safety and tolerability of 22 and 44 μM Lacripep ophthalmic solution versus placebo (vehicle) administered 3 times daily for 28 days in subjects with a history of ocular surface disease associated with primary Sjögren's syndrome. In addition, many dry eye signs and symptoms were assessed.

Lacripep (TearSolutions, Charlottesville, VA) is an investigational synthetic 19 amino acid peptide fragment of lacritin.[1,2] The 19 amino acid synthetic fragment retains all known biologic activity of the full 119 amino acid lacritin monomer[2] (Fig. 1). Lacritin was discovered by screening for natural protein agonists of tear secretion in vitro.[1]

Proteomic studies have revealed the active, monomeric form of lacritin to be downregulated in tears of patients suffering from many forms of dry eye disease, including aqueous-deficient, evaporative, contact lens–-related[3,4] but most strikingly in dry eye patients with primary[4,5] and secondary[2] Sjögren's syndrome.[6] Supplementation 3 times daily (TID) with 4 μM topical recombinant lacritin largely restored ocular surface homeostasis and reduced lacrimal gland inflammation in a mouse model of Sjögren's syndrome.[7]

Sjögren's syndrome is a chronic autoimmune disease of unknown etiology characterized by exocrine gland dysfunction either affecting only the eye and mouth

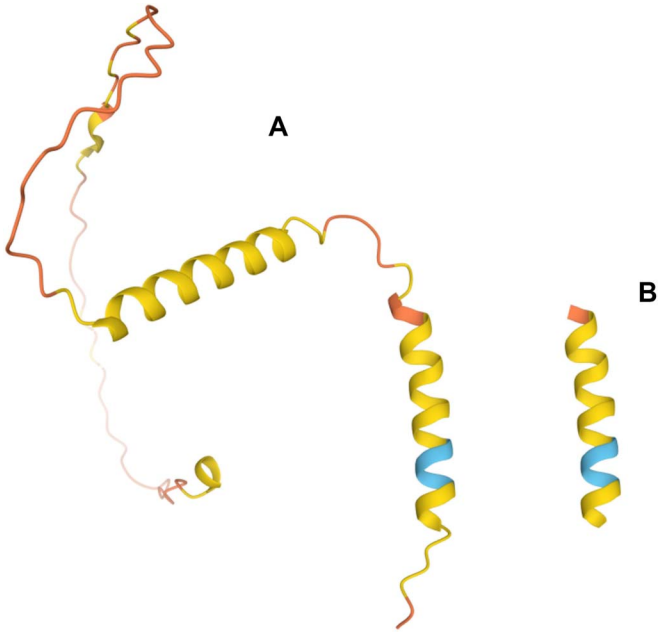


FIGURE 1. A, Mature Lacritin is a 119 amino acid glycoprotein found in human tears. B, Lacripep (a.k.a. "N-94/C-6") is a synthetic 19 amino acid peptide fragment of lacritin (Credit: Jeff Romano). (The full color version of this figure is available at www.corneajrnl.com.)

("primary Sjögren's syndrome") or with systemic involvement ("secondary Sjögren's syndrome"). Lymphocytic infiltration of lacrimal and salivary glands is the presumed pathophysiological mechanism,[8] but the incomplete clinical efficacy of topical immunosuppressive therapeutics suggests that other non–anti-inflammatory pathogenesis could have an important role. Many prior publications attest to the diverse effects that lacritin has on ocular surface homeostasis including mitogenic effects on epithelium and qualitative changes in the tear film involving lipids and mucins.[1,7,9–13] This suggests a potential role for lacritin in restoring homeostasis to the ocular surface affected by different types of dry eye disease. The absence or substantial deficiency of active monomeric lacritin (and of Lacripep-like fragments) in tears from most patients with Sjögren's syndrome[2] led to the choice of primary Sjögren's for this first-in-human clinical trial of topical Lacripep.

METHODS

Study Design

This was a multicenter, randomized, placebo-controlled, double-masked, parallel-group study conducted at 35 sites in the United States and approved by local institutional review boards. Written informed consent was obtained from all subjects after review of risks and benefits of participation. This study was conducted in accordance with the Health Insurance Portability and Accountability Act of 1996 and Declaration of Helsinki of 1996 and registered at ClinicalTrials.gov: NCT 03226444 (http://ClinicalTrials.gov, accessed January 15, 2022).

The study duration was 56 days, including a 14-day run-in period, 28-day active treatment period, and 14-day follow-up period (Fig. 2).

Study Protocol

Screening and Eligibility

At visit 1 (screening), informed consent was obtained from subjects and eligibility was determined requiring documentation of primary Sjögren's syndrome per the American-European Consensus Group Sjögren's Syndrome Criteria.[14] Subjects were aged at least 18 years with a history of dry eye–related symptoms and use of eye-wetting agents within the past 120 days. Major inclusion criteria at the screening and subsequent baseline visits included:

1. CFS total score ≥4 and <15 in the National Eye Institute Industry Workshop (NEI) scale.
2. Symptom Severity score of ≥40 using the Symptom Assessment in Dry Eye (SANDE) questionnaire.
3. Anesthetized Schirmer test score ≤5 mm wetting/5 minutes.
4. LGCS total score ≥5 using the NEI scale.

We excluded subjects with:

1. Active infectious ocular condition.
2. Ocular inflammatory conditions not related to dry eye syndrome.
3. Clinical evidence of cicatricial ocular surface disease.
4. Use of Restasis (topical ophthalmic cyclosporine) or Xiidra (topical ophthalmic lifitegrast) within 14 days before visit 1.

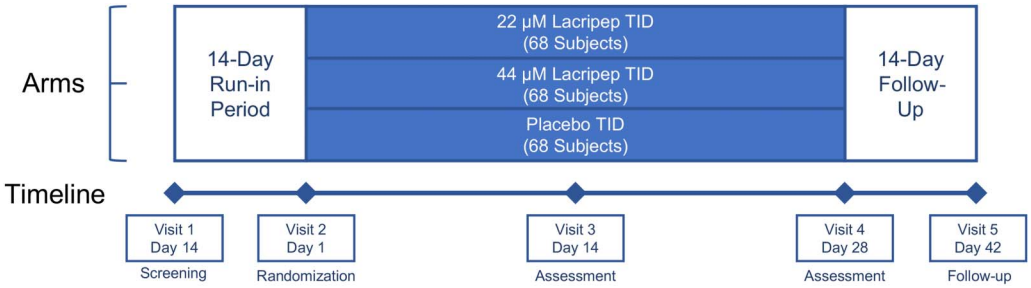


FIGURE 2. Study was of 56 days duration, including 28 days of treatment preceded by 14 days of run-in and followed by 14 days of wash-out. Measurements were collected at 5 scheduled visits. (The full color version of this figure is available at www.corneajrnl.com.)

TABLE 1. Sequence of Assessments

Procedure	Visit 1 Screening, Day −14 ± 2	Visit 2 Randomization, Day 1	Visit 3 Assessment, Day 14 ± 2	Visit 4 Assessment, Day 28 ± 2	Visit 5 Follow-Up, Day 42 ± 2
Efficacy assessments					
Corneal fluorescein staining	X	X	X	X	X
SANDE version 1	X	X	X	X	X
SANDE version 2			X	X	X
Individual Symptom Assessment (instantaneous)	X	X	X	X	X
Individual Symptom Assessment (reflective)			X	X	X
Lissamine green conjunctival staining	X	X	X	X	X
Tear film break-up time	X	X	X	X	X
Anesthetized Schirmer test	X	X	X	X	X
Safety assessments					
External eye examination	X	X	X	X	X
Slitlamp biomicroscopy	X	X	X	X	X
Best-corrected visual acuity	X	X	X	X	X
Intraocular pressure	X	X		X	X
Dilated ophthalmoscopy		X		X	
Adverse events	X	X	X	X	X

5. A history of collagen vascular disease, autoimmune disease, or rheumatic disease other than primary Sjögren's syndrome (Lupus, Rheumatoid Arthritis, etc.).
6. A history of or current anterior membrane dystrophy, corneal transplantation, corneal refractive surgery, or other recent ocular procedures.
7. Childbearing potential unwilling to use contraception or pregnant or breastfeeding.
8. Any physical or mental impairment that would have precluded participation and the ability to give informed consent.

Those eligible entered a 14-day run-in period involving instillation of 1 drop of single-masked placebo (vehicle) 3 times a day to each eye.

Randomization and Treatment

At visit 2 (baseline/randomization), eligibility was confirmed. All criteria were met in the same study eye. For each subject, the study eye was the one qualifying for study inclusion, or the one with higher baseline corneal fluorescein staining total score if both qualified, or the right eye if both eyes showed the same baseline score. Eligible subjects were randomly assigned to 1 of the 3 treatment groups: 1 of 2 Lacripep ophthalmic solution strengths (22 or 44 μM) or placebo (vehicle).

One drop of investigational product was administered 3 times a day (TID) to both eyes for 28 days. At visit 3 (week 2) and visit 4 (week 4), efficacy and safety evaluations were performed. Subjects who discontinued before visit 4 underwent visit 4 evaluations (early termination).

Fourteen-Day Follow-Up Period

After discontinuation of investigational product, there was a 14-day follow-up period during which subjects instilled 1 drop of Refresh Plus (Allergan, Dublin Ireland) TID to each eye.

At visit 5 (week 6 follow-up), efficacy and safety evaluations were performed.

Concomitant Medications/Therapies

Subjects whose records indicated the use of prohibited medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate prestudy washout period and/or during the 14-day vehicle run-in period before randomization were excluded from efficacy analyses before database lock.

Subjects had not received any investigational drug or device within 30 days of screening nor during the study except per-protocol. Subjects who were on systemic (oral) therapy for the treatment of Sjögren's syndrome must have been on stable systemic treatment defined as the same treatment for the immediately prior 90 days. The use of cyclosporin (compounded or Restasis Allergan, Irvine CA or Cequa, Sun Pharmaceuticals, Mumbai, India) or lifitegrast (Xiidra, Novartis, Basel, CH) within 14 days before the screening examination was prohibited. Subjects did not have alterations to (insertion or removal) punctal plugs in the study eye, within 14 days before the screening examination and during the entire study. Medications, topical or systemic, known to exacerbate dry eye were prohibited during this study.

Study Masking

Subjects were randomly assigned to receive either placebo or study drug. The placebo (vehicle) and Lacripep

containers during the double-masked treatment phase were identical in appearance. Study subjects and investigators and their staff were masked to the identity of treatment until the final database was locked.

Outcome Measures

Efficacy

The schedule of efficacy assessments is presented in Table 1. All efficacy assessments were performed in both eyes and by the same person if possible. Corneal fluorescein staining (CFS) was assessed in 5 regions (Central, Inferior, Superior, Temporal, and Nasal) on a 0 to 3 scale (total 0–15). Lissamine green conjunctival staining (LGCS) was assessed in 6 regions on a 0 to 3 scale (total 0–18). All sites were trained and tested on NEI scoring methodology.

The anesthetized Schirmer test was performed after instilling ~50 μL (one drop) of 0.5% proparacaine after drying the inferior cul-de-sac and recorded in mm of wetting over 5 minutes. Tear film break-up time was measured in seconds. The Symptom Assessment in Dry Eye (SANDE) inventory version 1 and version 2 measured patient-rated symptom severity and frequency using a visual analog scale. The Individual Symptom Assessments (instantaneous and reflective) measured patient-reported symptoms on a visual analog scale (VAS). The SANDE version 2 and Individual Symptom Assessments (reflective) asked patients to rate the difference in their symptoms as compared with their last clinic visit and were administered to subjects at day 14, 28, and 42 of treatment.

The primary efficacy measurement was a mean change from baseline to day 28 in CFS total score (NEI/industry workshop 0–15 scale, 0–3 scale in each of 5 regions) in the study eye. The key secondary efficacy measurement was a mean change from baseline to day 28 in Eye Dryness Score (VAS from 0 to 100 mm) from Individual Symptom Assessments.

The changes from baseline in CFS to day 14 and to posttreatment follow-up (day 42) were additional secondary measurements. Other secondary measurements included changes from baseline to day 14 and day 28 in the LGCS scores, TFBUT, and Schirmer tests. Secondary symptom measurements included changes from baseline to day 14 and day 28 in the SANDE and each of the Individual Symptom Assessments.

Safety

The schedule of safety assessments is presented in Table 1. Safety measurements included external eye examination, dilated ophthalmoscopy examination, intraocular pressure, slit-lamp biomicroscopy, and best-corrected visual acuity. If a subject had a diagnosis of or was noted to have Meibomian Gland Disease, the severity was rated.

All treatment-emergent adverse events (TEAEs), their severity, and relatedness to study drug were recorded.

Statistical Analysis

All analyses were performed using SAS (version 9.4, SAS Institute, Cary NC).

Analysis Sets

The intent-to-treat (ITT) set included all subjects who took at least 1 dose of investigational product, as indicated on the dosing record. All safety variables were analyzed using the safety analysis set, and only observed data were included (ie, missing data remained missing for the safety analysis).

The full analysis (FAS) set consisted of all subjects in the ITT set who met the prespecified inclusion criteria. Before database lock, several subjects were excluded from the FAS based on prospective eligibility exclusions and/or prospectively defined protocol violations.

Baseline and Safety Analyses

Demographic and baseline efficacy assessment parameters were summarized by the treatment group. Baseline ocular assessments were summarized for the study eyes. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA version 20.0, MedDRA MSSA, McLean, VA). Adverse events, and any adverse findings of standard safety examinations, were enumerated. Adverse event counts and percentages were summarized by the treatment group and the existence of any serious adverse events. Safety data were examined for trends among the treatment groups.

Prespecified Efficacy Analysis

The prespecified primary and secondary end point analyses were performed on the FAS.

The primary end points, difference between placebo and each of the 2 active dose groups in change from baseline to day 28 in the CFS total score, were tested first. A Bonferroni correction was used to control overall type 1 error (ie, these were formally tested to a significance level of $P < 0.025$). The key secondary end points (Eye Dryness

TABLE 2. Summary of Subject Disposition

	Placebo	Lacripep, 22 μM	Lacripep, 44 μM
Subjects randomized and treated (ITT set)	68	68	68
Failed exclusion criteria*	8	11	8
Subjects in full analysis set (FAS)	60 (100%)	57 (100%)	60 (100%)
Lost to follow-up during treatment	0 (0%)	1 (1.8%)	1 (1.7%)
Subject withdrew consent during treatment	0 (0%)	0 (0%)	1 (1.7%)
Subjects in FAS who completed treatment	60 (100.0%)	56 (98.2%)	58 (96.7%)
Lost to follow-up after treatment	1 (1.7%)	0 (0%)	0 (0%)
Subject withdrew consent after treatment	0 (0%)	0 (0%)	1 (1.7%)
Subjects in FAS who completed study	59 (98.3%)	56 (98.2%)	57 (95.0%)

*Subjects were treated but were excluded from primary analysis because of a prospectively defined exclusion criterion or protocol violation.

Score) were similarly tested using a Bonferroni gatekeeping procedure, that is, if the primary end points were met.

Next, the key secondary analysis was performed, with statistical inference contingent on the primary inference using the Bonferroni gatekeeper procedure. Other secondary efficacy end points were examined for any trends among treatment groups. All inferential summaries for these analyses were used for descriptive purposes. The point estimate and 95% confidence interval (CI) for the treatment differences were calculated along with the *P* value for the treatment comparison using a *t* test.

All 2-sample *t* tests conducted in the analyses did not assume equal variances, and the Satterthwaite approximation was used for different sample sizes compared. The last observation carried forward (LOCF) was used to impute missing values before day 28, except in the reflective individual symptom assessment, in which the patient explicitly compares symptoms with prior visits.

Post Hoc Efficacy Analysis

Post hoc, all primary and secondary end points were assessed for treatment effect controlling for baseline Eye Dryness Score (EDS) using analysis of covariance (ANCOVA). All ANCOVA models were fit using the PROC MIXED procedure in SAS. Post hoc analysis was also performed using all observed data in the ITT set, without imputation. Data from the ITT set were examined for trends and notable efficacy signals, using end point means ± standard errors, and *P* values from nonparametric Wilcoxon ranked-sum tests as a descriptor of statistical strength. Subgroups were then evaluated according to baseline EDS.

RESULTS

Subject Disposition

This study screened 350 subjects of which 204 subjects were enrolled for treatment, 68 in each of the 3 treatment groups (the ITT set). The FAS excluded 27 subjects based on exclusion criteria or protocol violations. Excluded treatment subjects reported the use of prohibited medications such as cyclosporin or lifitegrast during the run-in or displayed signs of comorbid autoimmune/connective tissue diseases characteristic of secondary Sjögren's.

The FAS consisted of 177 subjects with 60 in the placebo, 57 in the 22 μM Lacripep, and 60 in the Lacripep 44 μM groups. Five subjects in the efficacy analysis set failed to complete this study: 3 failed to complete the 28-day course of active treatment and 2 failed to complete the follow-up period (Table 2). In prespecified analyses, missing values from the patients withdrawing early were imputed using LOCF.

Subject Demographics

A detailed summary of demographic data is presented in Table 3. Female patients comprised 96% of the subjects. Subject mean age was 60 years with 87% identifying as white, most not Hispanic or Latino. There were no significant differences in demographics between the 3 study groups.

Baseline disease characteristics are summarized in Table 3. The subjects reported a baseline CFS total score of 9.0 ± 2.7 (mean ± SD). The baseline Eye Dryness Score was 65.5 ± 25.5 (mean ± SD). All 3 groups had similar baseline disease characteristics. Similar baseline characteristics were observed for the ITT set and FAS.

Efficacy Analysis

Prespecified Efficacy End points

The primary efficacy end point, mean change from baseline to day 28 in CFS total score in the study eye, was not met for either Lacripep 22 μM or Lacripep 44 μM. The primary analysis using 2-sample *t* test demonstrated no

TABLE 3. Demographic Information and Baseline Characteristics by Treatment Groups—Intent-To-Treat Set

	Placebo (n = 68)	Lacripep 22 μM (n = 68)	Lacripep 44 μM (n = 68)
Age (yr)			
Mean ± SD	60.0 ± 10.9	60.8 ± 11.2	60.1 ± 10.7
Sex			
Female	65 (95.6%)	65 (95.6%)	66 (97.1%)
Male	3 (4.4%)	3 (4.4%)	2 (2.9%)
Race			
White	59 (86.8%)	58 (85.3%)	60 (88.2%)
Black or African American	4 (5.9%)	4 (5.9%)	2 (2.9%)
Asian	2 (2.9%)	4 (5.9%)	4 (5.9%)
Native Hawaiian or other Pacific Islander	1 (1.5%)	0 (0%)	0 (0%)
American Indian or Alaskan Native	2 (2.9%)	2 (2.9%)	2 (2.9%)
Ethnicity			
Hispanic or Latino	8 (11.8%)	2 (2.9%)	5 (7.4%)
Not Hispanic or Latino	59 (86.8%)	66 (97.1%)	61 (89.7%)
Unknown	1 (1.5%)	0 (0%)	2 (2.9%)
Baseline CFS total score			
Mean ± SD	9.1 ± 2.8	9.3 ± 2.6	8.6 ± 2.8
Baseline Eye Dryness Score* (mm)			
Mean ± SD	65.6 ± 24.9	64.8 ± 25.6	66.0 ± 25.9
Baseline SANDE version 1 symptom severity score (mm)			
Mean ± SD	68.2 ± 16.5	69.5± 16.9	68.1 ± 17.2
Baseline LGCS total score			
Mean ± SD	11.6 ± 4.4	12.0 ± 4.3	11.8 ± 4.0
Baseline anesthetized Schirmer test score (mm)			
Mean ± SD	2.4 ± 1.8	2.3 ± 1.8	2.4 ± 1.5

*EDS from the Instantaneous Symptom Assessment.

significant difference between either Lacripep treatment compared with placebo ($P = 0.990$ for Lacripep 22 μM and $P = 0.074$ for Lacripep 44 μM). Analysis using an ANCOVA model adjusted for baseline value also demonstrated no significant difference.

No significant differences were observed in mean change from baseline to day 28 (visit 4) in Eye Dryness Score from Individual Symptom Assessments (instantaneous) between either Lacripep treatment compared with placebo ($P = 0.101$ for Lacripep 22 μM and $P = 0.922$ for Lacripep 44 μM). Post hoc analysis using an ANCOVA model adjusted for baseline value also demonstrated no significant difference.

Secondary Efficacy End points

Significant treatment difference favoring Lacripep 22 μM was observed for the mean CFS score change in the inferior region from baseline to day 14. The mean difference between the Lacripep 22 μM group and placebo group was −0.43 (95% CI: −0.75, −0.10), $P = 0.010$.

A significant treatment difference favoring Lacripep 22 μM was observed for the change in the burning/stinging symptom from baseline to Day 14 in the instantaneous symptom assessments. The mean difference between the Lacripep 22 μM group and placebo group was −14.01 (95% CI: −23.11, −4.92), $P = 0.003$.

Groups of significant changes in symptoms were observed in mean score differences comparing Lacripep with placebo on the Individual Symptom Assessments (reflective). Differences were observed between Lacripep 22 μM and placebo in the mean scores for the following symptoms at Day 42:

1. Eye dryness: mean difference = −8.34 (95% CI: −16.52, −0.16), $P = 0.046$.
2. Eye pain: mean difference = −7.48 (95% CI: −14.86, −0.10), $P = 0.047$.
3. Fluctuating vision: mean difference = −11.72 (95% CI: −19.39, −4.04), $P = 0.003$.

Differences were observed between Lacripep 44 μM and placebo in the mean scores for the following symptoms at day 28:

1. Eye dryness: mean difference = −8.54 (95% CI: −15.04, −2.03), $P = 0.011$.
2. Burning/stinging: mean difference = −10.55 (95% CI: −16.83, −4.27), $P = 0.001$.
3. Foreign body sensation: mean difference = −8.89 (95% CI: −15.91, −1.87), $P = 0.013$.
4. Eye discomfort: mean difference = −8.60 (95% CI: −15.31, −1.90), $P = 0.012$.
5. Eye pain: mean difference = −10.41 (95% CI: −17.68, −3.13), $P = 0.005$.
6. Fluctuating vision: mean difference = −9.96 (95% CI: −15.82, −4.11), $P = 0.001$.

There were no significant differences observed between placebo and the Lacripep treatment groups for change in the SANDE version 1 or version 2 scores from baseline to any subsequent visits. Similarly, no significant differences were observed in lissamine green conjunctival staining, anesthetized Schirmer test, and tear film break-up time tests.

Post Hoc Efficacy Analysis

The secondary end points yielded potential signals of treatment effect in the inferior region CFS changes and the burning/stinging symptom changes. These were repeated with ANCOVA analysis using the ITT set, showing a highly significant effect of baseline EDS. To illustrate, Figure 3 shows the inferior region CFS (ICFS) for the whole ITT set and for subgroups with baseline EDS from ≥40 to ≥80. The baseline EDS ≥60 subgroup showed the strongest treatment effect, while preserving 74/129 subjects (57%) in the sample set. The end points were re-evaluated in the subset of ITT subjects with EDS ≥60 at baseline. A significant treatment effect was seen in total and inferior CFS, the burning/stinging symptom, and in subregions of the conjunctiva using LGCS.

Corneal Staining

Improvement from baseline to day 14 in inferior region CFS score was statistically significant in the prespecified

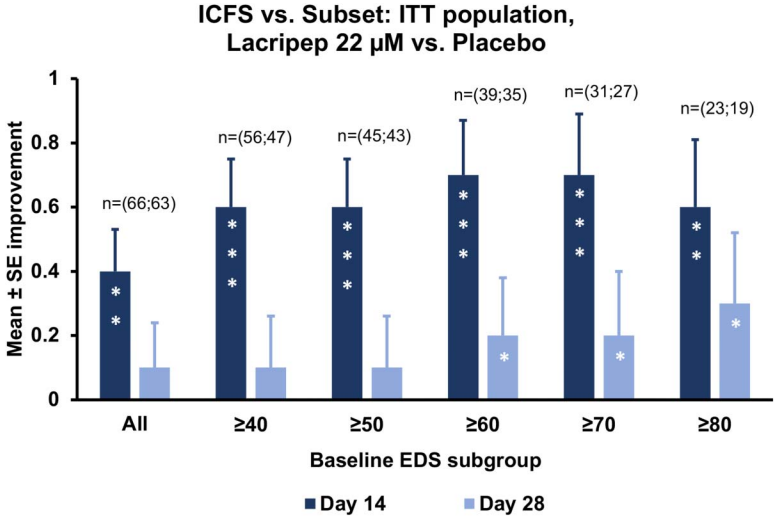


FIGURE 3. In post hoc analysis, the inferior corneal fluorescein staining (ICFS) score was computed for subsets of the ITT population according to baseline Eye Dryness Score (EDS). Mean and standard error of the results are plotted for each subset. The numbers of patients in each subset is indicated above the bars. The EDS ≥60 subgroup showed the statistically strongest effects ($P = 0.0001$ at 14 days and $P = 0.026$ at day 28). For their descriptive value, P value levels from post hoc Wilcoxon tests are indicated within bars (*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$). (The full color version of this figure is available at www.corneajrnl.com.)

analysis in the 22 μM Lacripep group versus placebo. The post hoc analysis shows a 0.4 improvement, $P = 0.005$ (Fig. 4A). In the subset of patients with baseline EDS ≥60, the effect is more pronounced (0.8 improvement, $P = 0.0001$) and a significant effect is seen at day 28 as well (0.4 improvement, $P = 0.026$). Positive (although not statistically significant) differences are seen in the higher dose group (Fig. 4B).

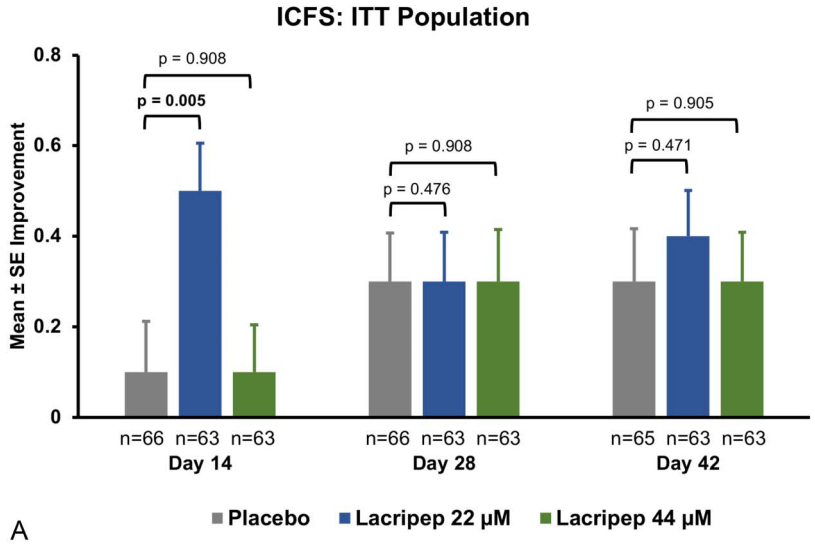
In the baseline EDS ≥60 set, the prespecified primary end point of total CFS score is significantly improved (1.2, $P = 0.03$) at day 14 for the 22 μM dose group versus placebo.

Individual Symptom Assessments (Burning/Stinging)

Improvement from baseline to day 14 in the burning/stinging symptom (reflective VAS rating) was statistically significant in the prespecified analysis in the 22 μM Lacripep group versus placebo. The post hoc analysis of the change in instantaneous rating of burning/stinging shows an 11.6-mm improvement on the VAS versus placebo, $P = 0.006$ (Fig. 5A). In the subset of patients with baseline EDS ≥60, a significant effect (14.0-mm improvement, $P = 0.027$) was shown at the same time point, and a significant effect is also shown in the higher dose group (14.2 mm, $P = 0.038$, Fig. 5B). Both dose groups trend better than the placebo group at day 28 and day 42 (not statistically significant).

Lissamine Staining

Improvement in LGCS was not statistically significant in the prespecified secondary end point analysis. However, in the subset of patients with baseline EDS ≥60, significant effects were seen. The change from baseline LCGS total score was improved for the 22 μM Lacripep group versus placebo at day 14 by 1.5 ($P = 0.017$). The same dose and time point showed a significant improvement in segment 1 (0.4, $P = 0.049$) and segment 5 (0.4, $P = 0.038$).



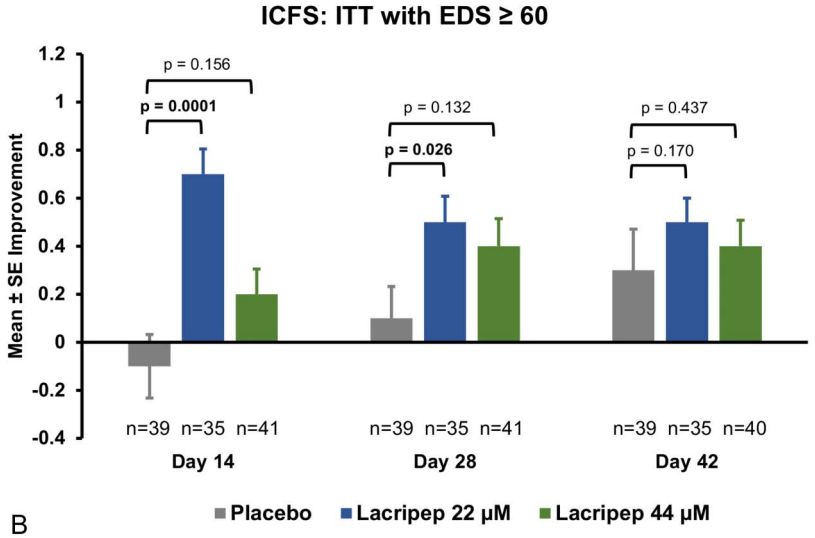


FIGURE 4. Post hoc analysis of the CFS sign. A, The primary end point of CFS score at day 28 was not met, but there was a significant treatment effect for the 22 μM dose at 14 days in the inferior corneal region. B, In the subset of subjects with a baseline EDS of ≥60, significant treatment effect was seen for the 22 μM dose at day 14 and day 28, falling off after washout at day 42; a positive but not significant effect was seen in the 44 μM dose group. (The full color version of this figure is available at www.corneajrnl.com.)

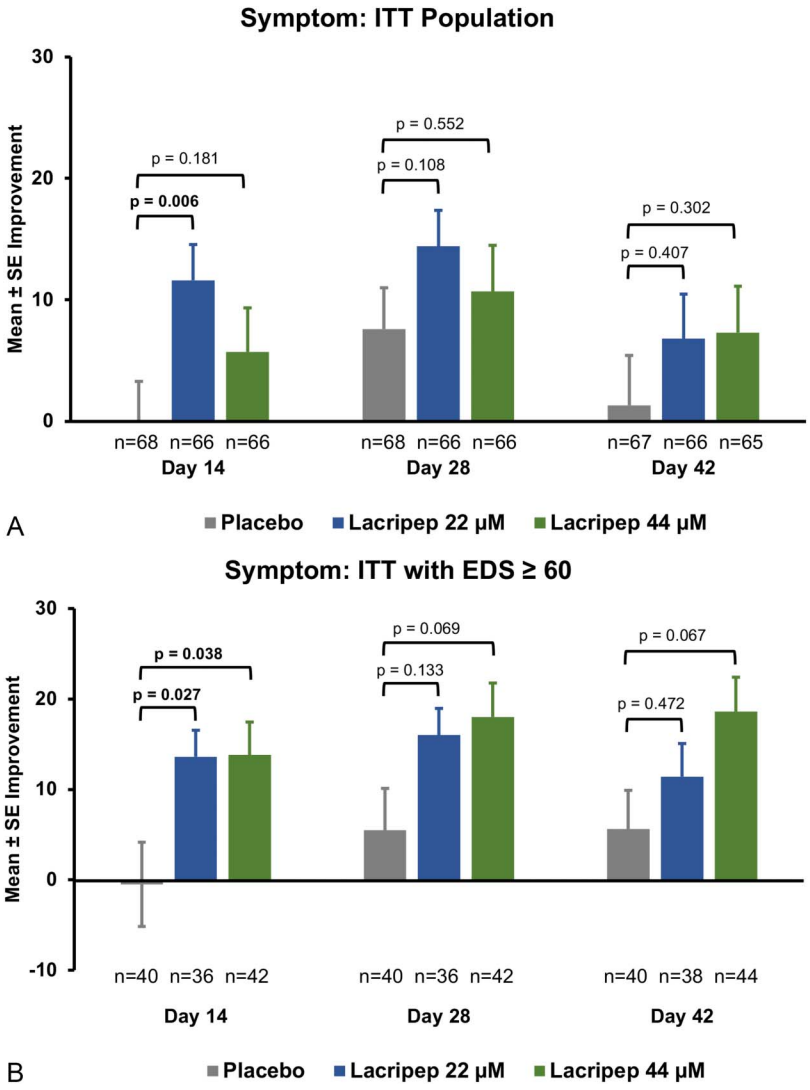


FIGURE 5. Post hoc analysis of the burning/stinging symptom. A, There was a significant treatment effect for the 22 µM dose at 14 days in the burning/stinging symptom. B, In the subset of subjects with a baseline EDS of ≥60, a significant treatment effect was seen for both doses at day 14. A positive but not significant effect was seen in both dose groups at day 28. (The full color version of this figure is available at www.corneajrnl.com.)

Safety Analysis

A total of 34 subjects of the 204 subjects (16.7%) reported at least 1 TEAE during this study (8 subjects in the placebo group, 11 subjects in the Lacripep 22 µM group, and 15 subjects in the Lacripep 44 µM group). Most subjects experienced TEAEs with mild severity, and no subject experienced TEAEs classified as severe. Only 1 subject experienced TEAE leading to study drug discontinuation, which was nonocular and unrelated to study drug. No serious adverse events and no deaths occurred during this study.

No significant differences between Lacripep and placebo were observed for other safety measures (slitlamp biomicroscopy and eye examination, intraocular pressure, best-corrected visual acuity, dilated ophthalmoscopy, and meibomian gland disease severity).

Ocular Adverse Events

The most commonly reported ocular TEAE was eye pain reported in 4 subjects (1.96%). A total of 10 subjects in this study (4.9%) experienced TEAEs suspected to be related to the study drug (4 subjects in the placebo group, 2 subjects in the Lacripep 22 µM group, and 4 subjects in the Lacripep 44 µM group). All TEAEs related to the study drug were ocular.

Table 4 summarize ocular TEAEs results. A total of 18 subjects reported ocular TEAEs in this study; 16 of these reported ocular TEAEs classified as mild in severity (4 subjects in the placebo group, 3 subjects in the Lacripep 22 µM group, and 9 subjects in the Lacripep 44 µM group). The remaining 2 subjects reported ocular TEAEs classified as moderate (1 subject in the placebo group and 1 subject in the Lacripep 44 µM group). During this study, the most commonly reported ocular TEAE was eye pain reported in 4 subjects (1.96%): 1 subject in the placebo group, 1 subject in the Lacripep 22 µM group, and 2 subjects in the Lacripep 44 µM group.

Nonocular Adverse Events

Table 5 summarize nonocular TEAEs results. A total of 19 subjects reported nonocular TEAEs in this study. Most

TABLE 4. Subjects With Ocular Treatment-Emergent Adverse Events—Safety Analysis Set

System Organ Class Preferred Term	Placebo (N = 68)	Lacripep 22 μM (N = 67)	Lacripep 44 μM (N = 69)*
Subjects with at least one ocular TEAE	5 (7.4%)	3 (4.5%)	10 (14.5%)
Congenital, familial, and genetic disorders	1 (1.5%)	0 (0%)	0 (0%)
Corneal dystrophy	1 (1.5%)	0 (0%)	0 (0%)
Eye disorders	4 (5.9%)	2 (3.0%)	6 (8.7%)
Conjunctival edema	0 (0%)	1 (1.5%)	0 (0%)
Conjunctivochalasis	0 (0%)	1 (1.5%)	0 (0%)
Corneal infiltrates	0 (0%)	0 (0%)	1 (1.4%)
Dry eye	0 (0%)	1 (1.5%)	0 (0%)
Exposure keratitis	0 (0%)	0 (0%)	1 (1.4%)
Eye irritation	1 (1.5%)	1 (1.5%)	1 (1.4%)
Eye pain	1 (1.5%)	1 (1.5%)	2 (2.9%)
Eyelid edema	0 (0%)	0 (0%)	1 (1.4%)
Foreign body sensation in eyes	2 (2.9%)	0 (0%)	0 (0%)
Photophobia	0 (0%)	0 (0%)	1 (1.4%)
General disorders and administration site conditions	0 (0%)	0 (0%)	2 (2.9%)
Instillation site pain	0 (0%)	0 (0%)	2 (2.9%)
Infections and infestations	0 (0%)	1 (1.5%)	2 (2.9%)
Conjunctivitis bacterial	0 (0%)	0 (0%)	1 (1.4%)
Conjunctivitis viral	0 (0%)	1 (1.5%)	1 (1.4%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	2 (2.9%)
Erythema	0 (0%)	0 (0%)	1 (1.4%)
Telangiectasia	0 (0%)	0 (0%)	1 (1.4%)

Adverse events were coded using MedDRA version 20.0. Treatment-emergent adverse events were defined as the date of onset is on or after the date of first dose of double-masked study drug. Related was defined as any adverse event with a 'Possibly Related" or 'Related" relationship to the study drug. Subjects were counted only once for each System Organ Class and Preferred Term with strongest relationship.

*One patient was mistakenly provided with the higher concentration test article for a portion of treatment and is thus counted with the higher dose group.

study subjects (13 of 19 subjects) reported nonocular TEAEs classified as mild in severity (2 subjects in the placebo group, 6 subjects in the Lacripep 22 μM group, and 5 subjects in the Lacripep 44 μM group). Six subjects reported nonocular TEAEs classified as moderate (1 subject in the placebo group, 3 subjects in the Lacripep 22 μM group, and 2 subjects in the Lacripep 44 μM group). During this study, the most commonly reported nonocular TEAE was viral upper respiratory tract infection reported in 6 subjects (2.9%): 1 subject in the placebo group, 4 subjects in the Lacripep 22 μM group, and 1 subject in the Lacripep 44 μM group. All nonocular TEAEs were not determined to be treatment-related.

DISCUSSION

Despite great progress in elucidating the pathophysiology of ocular surface disease, treatments largely focused on anti-inflammatory medications have not delivered adequate control of symptoms or fully normalized corneal and/or conjunctival staining. Similarly, only some treated patients have experienced normalization of their tear film break-up time, Schirmer test, tear MMP-9 levels, or tear osmolarity. We have not yet identified the core pathophysiologic process or comprehensively addressed the multiple pathogenic processes driving both symptoms and signs of OSD.

Understanding of ocular surface pathophysiology has evolved from understanding dry eye as an aqueous tear deficiency to focus on the inflammatory and immunomodulatory abnormalities affecting the ocular surface[15] that has continued to more detailed study of the metabolism of tears and the ocular surface.[3,4,16] Furthermore, there is now appreciation of the role of neural receptors including TRPM8 in the regulation of basal tearing and the perception of discomfort from ocular surface dysfunction.[17–19] Lacking are treatment options that address pathophysiology broadly to restore homeostasis and minimize inflammatory signals.

Lacritin acts broadly, including homeostatic functions and more specific actions on key elements of ocular surface physiology. It targets the cell surface[11,20] and affects signaling to promote autophagy that can be understood as targeted destruction of damaged organelles to forestall total death of the affected cells. More specifically, autophagy rids cells of inflammation-damaged proteins and organelles that are together toxic and would otherwise induce apoptosis.[9] Lacritin has been shown to trigger cell-selective mitogenesis[1,9,11] to promote corneal epithelial healing in mice[12] and human epithelia.[21] Topical lacritin substantially eradicated corneal lissamine green staining and cell surface boundary defects.[7]

Lacritin sustained basal and stimulatory tear secretory capacity in a biochemical screen of lacrimal proteins in a primary culture of isolated rat lacrimal acinar cells.[1,22] Confirmatory studies followed in other species,[23] and subsequent validations showed that all known biological activity of lacritin is mimicked by Lacripep.[2] Taking together, these activities with the selective deficiency of lacritin monomer in dry eye[5,24–28] suggest that low or absent lacritin may be a key risk factor for ocular surface disease. Based on the sum of these unique properties and effects of lacritin, we hypothesized that topical Lacripep could be a homeostatic restorative replacement therapy.

Discussion of Trial Results

In this first-in-human study, which was the largest ophthalmic trial to date in patients with primary Sjögren's with dry eye, both concentrations of Lacripep ophthalmic solution demonstrated an excellent safety profile. Adverse events were rare and occurred in similar frequency in placebo-treated patients. There were no serious or severe adverse events and no unexpected findings on a variety of eye examinations. The safety profile in this 28-day study is compatible with longer-term study of Lacripep therapy for dry eye.

The primary purpose of this study was to assess safety and tolerability but included prospective efficacy end points despite uncertainty about optimal drug concentration and

TABLE 5. Subjects With Nonocular Treatment-Emergent Adverse Events—Safety Analysis Set

System Organ Class Preferred Term	Placebo (N = 68)	Lacripep 22 μM (N = 67)	Lacripep 44 μM (N = 69)*
Subjects with at least one nonocular TEAE	3 (4.4%)	9 (13.4%)	7 (10.1%)
Blood and lymphatic system disorders	0 (0%)	0 (0%)	1 (1.4%)
Lymphadenopathy	0 (0%)	0 (0%)	1 (1.4%)
Gastrointestinal disorders	0 (0%)	0 (0%)	1 (1.4%)
Food poisoning	0 (0%)	0 (0%)	1 (1.4%)
Infections and infestations	3 (4.4%)	7 (10.4%)	3 (4.3%)
Bronchitis	0 (0%)	0 (0%)	1 (1.4%)
Localized infection	0 (0%)	1 (1.5%)	0 (0%)
Sinusitis	0 (0%)	2 (3.0%)	0 (0%)
Upper respiratory tract infection	0 (0%)	1 (1.5%)	0 (0%)
Urinary tract infection	2 (2.9%)	1 (1.5%)	1 (1.4%)
Viral upper respiratory tract infection	1 (1.5%)	4 (6.0%)	1 (1.4%)
Vulvovaginal mycotic infection	0 (0%)	0 (0%)	1 (1.4%)
Musculoskeletal and connective tissue disorders	0 (0%)	0 (0%)	1 (1.4%)
Muscle spasms	0 (0%)	0 (0%)	1 (1.4%)
Respiratory, thoracic, and mediastinal disorders	0 (0%)	1 (1.5%)	2 (2.9%)
Dyspnea	0 (0%)	0 (0%)	1 (1.4%)
Oropharyngeal pain	0 (0%)	1 (1.5%)	1 (1.4%)
Productive cough	0 (0%)	0 (0%)	1 (1.4%)
Skin and subcutaneous tissue disorders	0 (0%)	1 (1.5%)	1 (1.4%)
Dermatitis contact	0 (0%)	1 (1.5%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	1 (1.4%)

Adverse events were coded using MedDRA version 20.0. Treatment-emergent adverse events were defined as the date of onset is on or after the date of first dose of double-masked study drug. Related was defined as any adverse event with a 'Possibly Related" or 'Related" relationship to the study drug. Subjects were counted only once for each System Organ Class and Preferred Term with strongest relationship.

*One patient was mistakenly provided with the higher concentration test article for a portion of treatment and is thus counted with the higher dose group.

dosing. Total CFS score and Eye Dryness Score were prespecified as primary efficacy end points but not shown to significantly improve at these suboptimal doses. Secondary analyses and post hoc testing revealed several efficacy metrics in which Lacripep seemed to improve dry eye signs and symptoms. Inferior region CFS scores and the burning/stinging symptom rating improved in the lower (22 μM) dose group at day 14. Groupings of patient-assessed symptom changes were also positive at day 28 for the 44 μM dose and at day 42 (after washout) for the 22 μM dose group.

A post hoc analysis was performed to examine the dependence of these efficacy signals on baseline Eye Dryness Score (EDS). Improvements in sign and symptom end points were correlated with baseline EDS, and a reanalysis was undertaken in the subset of patients with baseline EDS ≥60 (representing moderate to severe dry eye disease). In these patients, there seems to be strong statistical evidence of a treatment effect in the lower dose (22 μM) after 14 days of treatment, in CFS, burning/stinging symptom rating, and LGCS. There are positive trends that may indicate efficacy at the higher dose and/or later time points, but for the most part, the response to 44 μM Lacripep was at or below baseline and thus below the 22 μM response, suggesting a bell-shaped (biphasic) dose response. It seems that Lacripep may have diminished effects at too low and too high concentration.

The bell-shaped dose response seen here with Lacripep is very common in human drug response. The mechanism may be analogous to that of the signaling response to fibroblast growth factor 2 (FGF2). It forms a receptor complex of a heparan sulfate proteoglycan (HSPG) and signaling receptor (fibroblast growth factor receptor 1 [FGFR1]) which conceptually approximates that of lacritin. FGF2–HSPG binding at lower concentrations precedes ligation of the complex with FGFR1 and induces signaling; but at higher concentrations, FGF2 binds FGFR1 directly and prevents signaling.[29] The diminished efficacy at 28 days versus 14 days may reflect differing time scales of the biphasic dose response but requires further research.

We hypothesize that further dose optimization may dramatically improve treatment response, given the lower optimal doses seen in preclinical and cell studies. In normal rabbits, for example, 4 μM human lacritin was optimal over a 0 to 8 μM dose range to enhance basal tearing four-fold over the comparators.[30] Other in vitro human cell assays have also shown a bell-shaped response to lacritin, with effects diminishing at lower and higher than optimal doses.[9,10]

Multiple trials have failed to show significant improvement in both signs and symptoms in a single trial. For example, lifitegrast was assessed in separate trials for signs[31] and symptoms[32,33] of dry eye syndrome. Nonetheless, data from this study indicate both sign and symptom improvement worthy of further joint study in the same population of dry eye patients. The results recognized on *post hoc* analysis recapitulate and confirm what has been observed in previous studies of dry eye treatment. CFS and LGCS have been established as signs relevant to the assessment of dry eye treatment. Improvement in inferior CFS, in particular, is a sensitive marker of disease regression for which there is precedent in the lifitegrast studies, where statistically significant effects on inferior CFS were also observed in patients with baseline EDS ≥ 60.[31] This subset reflects moderate to severe dry eye, where medical need is high and inferior CFS changes on treatment are valid and reproducible.

Study Limitations

This study established initial safety data and clinical experience for this novel lacritin-based treatment for dry eye. Signals of efficacy were also observed, but with several limitations. The initial hypotheses, that we would see a treatment effect in total CFS score and in the eye dryness symptom, were not born out with statistical significance. The sign (ICFS) and symptoms (particularly the burning/stinging rating) which did seem significant must be retested prospectively. We did not see that the LOCF data imputation

used in the prespecified end points and the missing data from post hoc analysis would have changed any conclusions here, but diligence must be exercised in subsequent studies.

CONCLUSIONS

This study showed evidence of efficacy in both signs and symptoms of dry eye. These seemed stronger at earlier time points and at the lower dose tested. The concentrations used in this first clinical study of Lacripep based on the latest in vivo and in vitro studies were likely too high for optimal therapeutic benefit, based on best estimates of dilution and residence time in humans. In vitro data and the relatively greater treatment response at the lower dose suggest that lower concentrations should be explored.

In this first-in-human study of Lacripep, a broad regulator of ocular surface homeostasis, safety data, and efficacy signals was established to guide further study. Lacripep has potential for the treatment of dry eye and should be studied further with different dosing concentrations, time scales, and patient populations.

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