Results From a Multicenter, Open-label, Phase 4 Study of Repository Corticotropin Injection in Patients With Treatment-resistant Severe Noninfectious Keratitis

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Introduction

Background

- Keratitis is a painful inflammation of the cornea and is a significant cause of ocular morbidity[1,2]
  - If untreated, keratitis can lead to permanent corneal damage[3]
- Noninfectious keratitis is commonly treated with lubricants, corticosteroids, and immunosuppressants
- However, few treatment options are available for advanced noninfectious keratitis that has not improved after treatment with standard-of-care therapies

Repository Corticotropin Injection (RCI)

- RCI is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides[4]
- RCI engages all 5 melanocortin receptors on immune cells and tissues throughout the body and has demonstrated direct immunomodulatory and indirect anti-inflammatory effects[5]
- RCI is approved by the US Food and Drug Administration for the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, including keratitis[4]

Objective

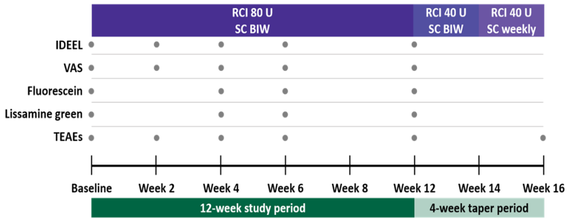
- This multicenter, open-label, phase 4 study evaluated the efficacy and safety of RCI for the treatment of refractory severe noninfectious keratitis that did not improve after treatment with first-line therapies (ClinicalTrials.gov NCT04169061)

Methods

Study Design and Data Collection

- Adults with severe noninfectious keratitis that did not improve after treatment with topical cyclosporin, lifitegrast, or any immunosuppressant were enrolled in the study
- Patients or their caregivers administered 80 U of RCI twice weekly for 12 weeks followed by a tapering period of 4 weeks **(Figure 1)**
- The following efficacy assessments were conducted at baseline and throughout the study **(Figure 1)**:
  - Impact of Dry Eye on Everyday Life (IDEEL) questionnaire
  - Visual Analog Scale (VAS) for Eye Dryness
  - Ora Calibra™ Corneal and Conjunctival Staining Scales using fluorescein and lissamine green
- Safety was assessed via treatment-emergent adverse events (TEAEs) and serious TEAEs collected throughout the study **(Figure 1)**

Figure 1. Study Design and Data Collection



Abbreviations: BIW, twice weekly; IDEEL, Impact of Dry Eye on Everyday Life; RCI, repository corticotropin injection; SC, subcutaneously; TEAE, treatment-emergent adverse event; VAS, Visual Analog Scale.

Outcomes

- The primary efficacy endpoint was the proportion of patients with ≥12-point improvement in the IDEEL symptom bother score at week 12
- Other efficacy endpoints included proportions of patients with ≥20%, ≥30%, and ≥50% improvement in the IDEEL symptom bother score at week 12 and change from baseline to week 12 in VAS and sums of the Corneal and Conjunctival Staining Scales
- Safety endpoints were the percentage of patients who experienced any TEAE or serious TEAE throughout the study period

Statistical Analyses

- Efficacy endpoints were analyzed in the modified intent-to-treat (mITT) population (all patients who received ≥1 dose of RCI and contributed any postbaseline efficacy data)
- Safety endpoints were analyzed in the safety population (all patients who received ≥1 dose of RCI)
- 95% confidence intervals (CIs) were calculated based on normal approximation

Results

Demographics

- The mean (standard deviation [SD]) age of the mITT population (N=36) was 63.3 (10.2) years
- Most patients were female (71.4%), White (80.0%), and not of Hispanic or Latino ethnicity (94.3%)
- All patients had keratitis in both eyes; the mean (SD) and median durations of keratitis for all patients were 4.4 (5.4) and 2.6 years, respectively

IDEEL Symptom Bother Module

- At baseline, the mean (SD) IDEEL symptom bother score in the mITT population was 65.4 (15.5)
  - At week 12 after RCI initiation, 50.0% (95% CI [33.2%, 66.8%]) of patients had a ≥12-point improvement
  - 52.9% (95% CI [36.2%, 69.7%]) had a ≥12-point improvement as early as week 2
- The proportions of patients who experienced ≥20%, ≥30%, or ≥50% improvement in the symptom bother score at week 12 after starting RCI therapy are listed in Table 1

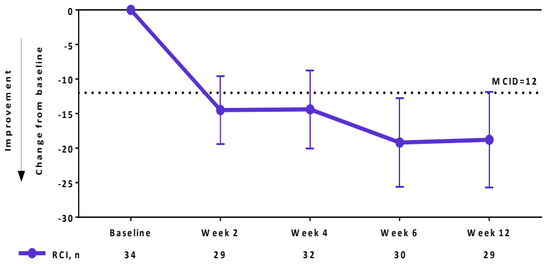
Table 1. Proportions of Patients Who Experienced ≥20%, ≥30%, or ≥50% Improvement in the IDEEL Symptom Bother Score

	Week 12 (n=34)					
	≥ 20%		≥ 30%		≥ 50%	
	%	95% CI, %	%	95% CI, %	%	95% CI, %
Symptom bother	50.0	(33.2, 66.8)	44.1	(27.4, 60.8)	14.7	(2.8, 26.6)

Abbreviation: IDEEL, Impact of Dry Eye on Everyday Life.

- Mean changes from baseline in the symptom bother score exceeded the minimal clinically important difference threshold at every time point (Figure 2)

Figure 2. Mean (95% CI) Change From Baseline in the IDEEL Symptom Bother Score



MCID is based on the threshold proposed by Fairchild et al.[6]
Abbreviations: IDEEL, Impact of Dry Eye on Everyday Life; MCID, minimal clinically important difference; RCI, repository corticotropin injection.

VAS

- At 12 weeks after RCI initiation, all symptoms assessed by the VAS had improved from baseline (Table 2)
- The most pronounced improvements were observed for eye dryness and eye discomfort

Table 2. Change From Baseline for Each Item of the VAS

	Baseline (n=29)		Week 12 (n=26)		
	Mean	SD	Mean	SD	95% CI
Eye dryness	77.6	18.2	−22.2	25.6	(−32.6, −11.8)
Burning/stinging	45.3	29.1	−13.5	24.3	(−23.3, −3.7)
Itching	44.1	29.5	−10.1	27.3	(−21.1, 0.9)
Foreign body sensation	50.9	27.8	−17.7	22.5	(−26.7, −8.6)
Eye discomfort	71.3	20.3	−23.9	25.4	(−34.2, −13.7)
Photophobia	57.0	25.7	−19.5	26.5	(−30.2, −8.8)
Pain	34.5	23.3	−15.0	20.2	(−23.1, −6.9)

Abbreviations: SD, standard deviation; VAS, Visual Analog Scale.

Corneal and Conjunctival Staining Scales

- At baseline, the mean (SD) fluorescein corneal sum in the mITT population was 5.3 (0.9)
  - Improvements from baseline were observed as early as week 4 after initiation of RCI treatment (−1.0 [1.5]; 95% CI [−1.5, −0.4]) and were sustained through week 12 (−1.1 [1.4]; 95% CI [−1.6, −0.6])
- At baseline, the mean (SD) lissamine green conjunctival sum in the mITT population was 3.5 (1.3)
  - Improvements from baseline were observed as early as week 4 after initiation of RCI treatment (−0.6 [0.9]; 95% CI [−0.9, −0.2]) and were sustained through week 12 (−0.7 [1.4]; 95% CI [−1.2, −0.2])

Safety

- Of patients in the safety population (N=36), 33.3% experienced ≥1 TEAE after initiation of RCI treatment; most TEAEs were single incidences (Table 3)
- No increase in intraocular pressure was observed
- One serious TEAE of intentional overdose was reported but was not related to RCI treatment

Table 3. Safety Results

	Safety population[a] (N=36)
TEAEs, No. (%)	
Hypertension	2 (5.6)
Abdominal pain	1 (2.8)
Ankle fracture	1 (2.8)
Blurred vision	1 (2.8)
Double vision	1 (2.8)
Fever	1 (2.8)
Increased viscosity of upper respiratory secretions	1 (2.8)
Intentional overdose	1 (2.8)
Irritability	1 (2.8)
Polymyalgia rheumatica	1 (2.8)
Weight gain	1 (2.8)
Wrist fracture	1 (2.8)
Upper respiratory tract infection	1 (2.8)

[a]All patients who received ≥1 dose of RCI.
Abbreviations: RCI, repository corticotropin injection; TEAE, treatment-emergent adverse event

Conclusions

- Results of this open-label study showed that 80 U of RCI twice weekly for 12 weeks was associated with rapid and sustained improvements in the symptoms of persistent severe noninfectious keratitis that had previously not responded to standard-of-care therapies
- No new safety signals for RCI were identified
- These results support the utility of RCI as a safe and effective treatment option for refractory severe noninfectious keratitis

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