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Systematic Literature Review on the Effect of Cenegermin on Corneal Sensation and Innervation in Patients with Neurotrophic Keratopathy

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Abstract

Purpose: Neurotrophic keratopathy (NK) results from trigeminal nerve impairment, leading to loss of corneal sensation (CS), epithelial breakdown, and in advanced stages, stromal ulceration or perforation. Cenegermin, a recombinant human nerve growth factor, is the first and only FDA-approved therapy for NK, although existing studies are limited by small sample sizes. This systematic literature review evaluated cenegermin's effects on CS and corneal innervation (CI) in patients with NK.
Methods: English-language studies published between August 2018 and June 2024 measuring CS or CI after cenegermin treatment for NK were identified through PubMed and Embase. For studies reporting quantitative data, sample size-based weighting was applied to each study's reported or derived mean change. Weighted means were calculated by NK stage or overall, where applicable.
Results: A total of 25 studies met the inclusion criteria. The pooled mean age was 61.8 years (range: 2–93 years). Most included patients with stage II (moderate; 19 studies) and stage III (severe; 17 studies) NK. Across 8 studies reporting quantitative CS outcomes and 3 studies reporting quantitative CI outcomes, the weighted mean improvement from baseline to 8 weeks post-treatment was 116.5% for CS (range: 78.3%–259.3%) and 64.5% for CI (range: 39.1%–188.9%).
Conclusion: An 8-week course of cenegermin led to improvements in CS and CI in patients with NK, with greater relative gains observed among those patients with more severe disease. While study design heterogeneity and small sample sizes may limit the generalizability of these findings, the data support cenegermin's role in promoting corneal nerve regeneration.

Keywords: neurotrophic keratitis, cenegermin, corneal sensation, corneal innervation

Introduction

Neurotrophic keratopathy (NK) is a rare, degenerative corneal disease. It has been classified as an orphan disease (ORPHA137596), affecting 5 or fewer persons per 10,000.[1] Incidence is highest among older adults, particularly those older than 60 years.[2] Common causes of NK include viral infections (herpes simplex and herpes zoster viruses), diabetes mellitus, and ocular surgeries.[2–4]

NK is characterized by an alteration in corneal innervation (CI) that leads to impairment of corneal sensation (CS) and trophic function, and therefore degeneration of the corneal epithelium.[1] CI is essential for maintaining the health of the epithelium, supporting cell growth, and promoting wound healing.[5] Loss of sensory nerve function also weakens the protective lacrimation and blink reflexes, further compromising the ocular surface.[6]

The Mackie classification system is the most widely used system to stage NK based on the severity of corneal impairment.[7] In stage I, patients show early signs of disease, including punctate epithelial defects, surface irregularity, and superficial neovascularization, which are often detected with vital dye staining. Stage II is marked by persistent corneal epithelial defects (PCEDs) of the cornea that do not extend into the stroma. PCEDs usually have a smooth, oval appearance with rolled edges due to failed corneal healing as a result of

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loss of trophic support. Stage III is the most severe form of NK and is defined by corneal ulceration, stromal thinning or melting, and in extreme cases, perforation—all of which pose a serious threat to vision.[8–10]

Cenegermin is a topical recombinant form of human nerve growth factor that promotes epithelial regeneration, supports sensory nerve survival, and stimulates regeneration of the trigeminal nerve.[7,9,11] It is the first treatment targeting the underlying disease mechanism rather than only managing signs and symptoms.[12] Cenegermin was approved by the European Medicines Agency (EMA) in 2017 and the US Food and Drug Administration (FDA) in 2018.[13,14] Two phase 2 randomized clinical trials (NGF0212 [REPARO] and NGF0214) demonstrated that patients treated with cenegermin over an 8-week period had statistically significant reductions in lesion size and disease progression compared with vehicle.[15–17] A subsequent phase 4 (DEFENDO; NCT04485546) prospective, open-label, uncontrolled clinical trial in patients with stage I NK found that 84.8% (28/33) of patients experienced corneal epithelial healing at 8 weeks, with 95.2% of patients maintaining results at 24 weeks post-treatment.[18]

Cenegermin's pivotal trials (NGF0212 [REPARO] and NGF0214) demonstrated its efficacy and safety[16]; however, CS and CI results are mixed in the literature, with some studies showing improvements and others not reaching statistical significance. These conflicting data highlight the need for a systematic literature review to comprehensively assess cenegermin's impact on both CI and CS in patients with NK.

Methods

Search strategy

We conducted a systematic literature search to identify studies evaluating CI and CS in patients with NK treated with topical cenegermin. We followed literature review best practices as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[19] with study aims framed as per the Population, Intervention, Comparison, Outcomes (PICO) framework. We defined the population of interest as humans (any age) diagnosed with NK (any stage) in any country. The intervention of interest was treatment with cenegermin, and a comparison group was not required. Outcomes of interest included changes in CI assessed by nerve morphology and density using *in vivo* confocal microscopy, and changes in CS measured using a Cochet–Bonnet esthesiometer (CBE) or qualitative testing (e.g., cotton wisp, dental floss). We limited inclusion to studies written in English, published in medical journals after cenegermin's US approval on August 22, 2018, and excluded review articles. Search terms were developed in collaboration with a medical librarian (see Table 1). MEDLINE (via PubMed) and EMBASE were searched on June 17, 2024, to identify eligible articles published between August 22, 2018, and June 17, 2024. Together, these databases capture the majority of published ophthalmology research on NK. The study protocol, entitled "Systematic Literature Review (SLR) on the Effect of Nerve Growth Factor (NGF) on Corneal Innervation in Neurotrophic Keratitis: Analytic Plan," was registered at the Center for Open Science's OSF literature review registry: https://osf.io/sez23/overview.[20]

Study selection

Two reviewers independently screened publications in two phases (title/abstract and full-text) using the systematic review software Nested Knowledge (version 1.3). The initial search retrieved publications from PubMed and EMBASE, which were imported into Nested Knowledge for screening. Only one reason for exclusion was required at each screening stage. We included articles reporting data on either CI or CS in patients of any age with NK treated with cenegermin. Patients were not excluded for using concomitant medications or required to use cenegermin as first-line therapy. In multigroup studies, a comparison or control group was not required. Outcomes of interest included changes in CI and CS using quantitative or qualitative methods. Case reports involving a single patient, literature reviews, and non-English-language studies were excluded. Full-text screening was performed on 53 articles, ultimately yielding 25 included studies. Duplicates were automatically identified and flagged for removal by the Nested Knowledge platform, and we subsequently verified that all duplicates had been removed. We cross-checked institutions and study periods to minimize overlap of patient data.

Data abstraction

All included studies were abstracted by one reviewer and verified by a second to ensure accuracy. We abstracted key information, including study identification and metadata (e.g., title, first author, publication year), study design characteristics (e.g., study research design type, study limitations, number of patients), population details (e.g., NK severity stage, patient age, race/ethnicity, gender), intervention details (e.g., cenegermin dose and regimen), and CS and CI measures (e.g., method used, units, time points). For CS, we abstracted change from baseline, percent change, quadrant-level change,

Table 1. Search Terms Used

Publication database[a]	*Search Terms Used*[b]
PubMed	(Oxervate OR "cenegermin" [Supplementary Concept] OR cenegermin OR "Recombinant Proteins/therapeutic use"[MeS.H] OR "Nerve Growth Factor/therapeutic use"[MeSH]) AND (keratitis[Mesh] OR "Neurotrophic keratitis" OR "Neurotrophic keratopathy" OR "refractory corneal ulcer*" OR "neurotrophic ulcer*" OR "impaired corneal innervation" OR "chronic keratitis" OR "ulcerative keratitis")
EMBASE	(Oxervate OR 'cenegermin'/exp OR cenegermin OR 'recombinant protein'/exp/dm_th OR 'nerve growth factor'/exp/dm_th) AND ('keratitis'/exp OR 'Neurotrophic keratitis' OR 'Neurotrophic keratopathy' OR 'refractory corneal ulcer*' OR 'neurotrophic ulcer*' OR 'impaired corneal innervation' OR 'chronic keratitis' OR 'ulcerative keratitis')

[a]Search date: June 17, 2024.
[b]All searches were limited to a 5-year period (August 22, 2018–June 17, 2024).

and statistical significance; for CI, we abstracted change from baseline in nerve density or length, percent change, and qualitative descriptors where applicable. We further conducted a risk of bias (ROB) assessment using the National Heart, Lung, and Blood Institute (NHLBI) tools for Quality Assessment for Observational Cohort and Cross-Sectional Studies, and Controlled Intervention Studies.

Data analysis

In addition to a descriptive synthesis, we conducted a quantitative analysis to characterize changes in CS and CI across studies. Because the review was descriptive and did not pool effect estimates, statistical heterogeneity metrics were not applicable. Of the included articles, 8 reporting CS outcomes and 3 reporting CI outcomes met the criteria for quantitative analysis, as they provided quantifiable data in the text or tables rather than in figures alone. For cases where data were reported in figures and values were not provided, we reached out to the corresponding authors to obtain missing data or confirm unclear data; none responded.

We abstracted and standardized reported values, converted medians to means using the Meta Convertor calculator as needed,[21] and applied sample size-based weights to estimate overall and stage-specific weighted mean changes from baseline to 8 weeks post-treatment initiation. Eight weeks was selected because it was the most consistently reported early post-treatment time point across studies and corresponds to a full course of cenegermin treatment. We accounted for differences in measurement techniques and reporting formats to enable consistent cross-study comparison, using Microsoft Excel.

Results

Search and screening overview

A total of 165 records were identified through searches of PubMed and EMBASE. After removing 48 duplicates, 117 unique records remained and underwent abstract-only screening. Of these, 62 were excluded for reasons such as being literature reviews, lacking outcomes of interest, or other factors, as described in Figure 1. The remaining 55 studies proceeded to a full-text review, during which 30 were excluded as they did not meet the full inclusion criteria. Ultimately, 25 studies met all the inclusion criteria and were included in the final review (see Fig. 1).

Summary of included articles

Included studies comprised 18 case series, 3 cohort studies, 2 randomized controlled trials, 1 case–control study, and 1 uncontrolled phase 4 trial. Most studies included data on CS ($n = 21$), while few studies assessed CI ($n = 8$).

Studies were conducted in several countries, with the United States and Italy accounting for the largest number of studies (n = 10 each). Other countries included Germany, Spain, China, France, Poland, Belgium, Hungary, Portugal, and the United Kingdom. Sample sizes ranged from small case series (2–5 patients) to larger clinical trials enrolling up to 156 patients (see Table 2).

Across 24 studies that reported gender distribution, 319 females (62.5%) and 191 males were included. The pooled mean age among the 19 studies that reported both mean age and sample size was 61.8 years. Among studies that reported NK etiology, the most common etiologies were herpetic eye disease (n = 137 patients), surgical procedures (n = 99 patients), including post-neuroma surgery and ocular surgeries, and diabetes mellitus ($n = 52$ patients). Among patients with other eye disorders, dry eye was the most commonly reported condition ($n = 62$ patients). Other frequently reported ocular conditions or procedures included intraocular lens implantation (n = 19 patients), Sjögren's disease (n = 10 patients), and complications related to Graves' disease, limbal stem cell deficiency, ocular surface injury or inflammation,

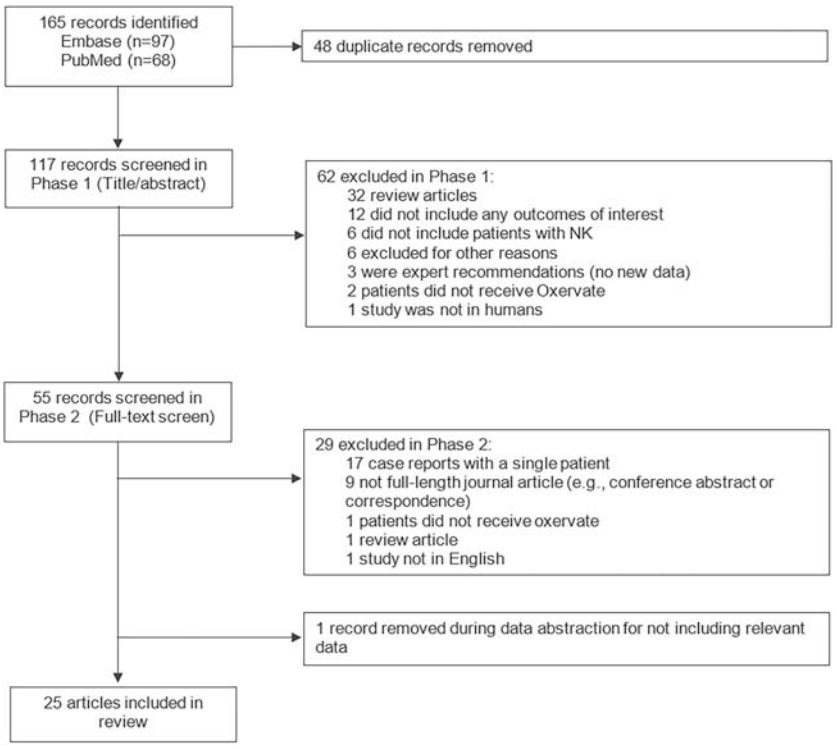

FIG. 1. Flow diagram depicting the literature review process and studies identified.

Table 2. All Included Studies

First author	Country	Study design	Sample size	NK Stage(s)	Funding	Data included	
						CS	CI
Qu etal., 2024[22]	China	Cohort study, prospective	9 patients, including pediatrics (age range: 16–54 years)	II, III	This study was supported by fund of Investigator-Initiated Research 2021–1211 of Dompe' farmaceutici S.p.A. The journal's rapid service fee was funded by Peking University Third Hospital.	(+)	
Hamrah et al., 2024[18]	United States	Phase 4 uncontrolled trial, prospective	37 patients (8 discontinued)	I	Funding for this study was provided by Dompé farmaceutici S.p.A. Institutional review board approval was obtained for the study protocol, protocol amendments, informed consent forms, and related documents at each center (Sterling IRB, 8203-DJSchanzlin, 8203-EJHolland, 8203-GJBerdy, 8203-MMassaroGiordano; and WCG-WIRB, 20202809).	(+)	
Dai et al., 2024[23]	United States	Case series[b]	14 patients	I	Supported, in part, by a research grant from Fight for Sight. One of the authors was a consultant to Dompé US	(+)	
Balbuena-Pareja et al., 2023[24]	United States	Case–control, retrospective longitudinal	25 patients	I, II, III	Supported by Dompé US; Massachusetts Lions Eye Research Fund, Inc. (PH); the Lions Club International Foundation (PH); Tufts Medical Center Institutional Support, Boston, Massachusetts (PH); Research to Prevent Blindness, Inc. Studies involving humans were approved by the Tufts Institutional Review Board.	(+)	(+)
Bruscolini et al., 2022[25]	Italy	Case series[b]	18 patients	II, III	Dompé Farmaceutici S.p.A provided an unrestricted medical writing grant. The sponsors or funding organizations had no role in the design or conduct of this research. This study was approved by the Investigational Review Board (IRB) of University Sapienza of Rome, Italy (IRB number 5338) with informed consent obtained at follow-up visits.	(+)	(+)

(*continued*)

TABLE 2. (CONTINUED)

First author	Country	Study design	Sample size	NK Stage(s)	Funding	Data included	
						CS	CI
Pedrotti et al., 2022[26]	Italy	Case series[a]	18 patients	II, III	Reported receiving no funding. Received approval from the Institutional Ethics Committee of Verone and Rovigo and obtained informed consent from all participants.	(+)	(+)
Saricay et al., 2022[27]	United States	Chart review, retrospective	17 patients	I	Supported by Dompe US; Massachusetts Lions Eye Research Fund, Inc. (P.H.); the Lions Club International Foundation (P.H.); Tufts Medical Center Institutional Support, Boston, Massachusetts (P.H.); and Research to Prevent Blindness, Inc. Approved by the Tufts Medical Center/ Tufts University Health Sciences Institutional Review Board. Informed consent was not obtained since this is a retrospective chart review.		(+)
Elhusseiny et al., 2022[28]	United States	Chart review, retrospective	4 patients, all younger than 18 years	I, II	Reported receiving no financial support for the research, authorship, and/or publication of the article.		(+)
Roszkowska et al., 2022[29]	Italy	Case series[a]	8 patients with stage II, 13 patients with stage III	II, III	Received no financial support from any public or private sources for the research, authorship, and/or publication of this article.	(+)	
Epitropoulos et al., 2022[30]	United States	Case series[b]	4 patients	I	Funded by a Dompé investigator-initiated research grant. Reviewed by Sterling IRB. Written consent did not need to be obtained.	(+)	
Garcia-Delpech et al., 2022[31]	Spain	Case series	5 patients	II, III	Funding support was provided by Dompé Farmaceutici SpA. Written informed consent was obtained from all patients. Ethical approval was not required.	(+)	
Bu et al., 2022[32]	Germany	Case series	4 patients, including 1 pediatric patient	II, III	Funding source was unclear. Consent to publish the case report was not obtained. IRB approval was obtained. Written consent to publish potentially identifying information was obtained from the patient(s) or their legal guardians.	(+)	

(*continued*)

TABLE 2. (CONTINUED)

First author	Country	Study design	Sample size	NK Stage(s)	Funding	Data included	
						CS	CI
Meduri et al., 2022[33]	Italy	Case series	11 patients	II, III	Funding source was not listed. Studies involving human participants were reviewed and approved by the Ethics Committee of the University Hospital of Messina. Patients provided their written informed consent.	(+)	
Sacchetti et al., 2022[34]	Italy	Cohort study, retrospective	30 patients	II, III	Open access funding provided by Università degli Studi di Roma La Sapienza. Two of the authors were consultants/advisors for Dompé. Approved by the Institutional Ethics Committee of Sapienza University of Rome. Informed consent was obtained from all individual participants.	(+)	
Inferrera et al., 2022[35]	Italy	Chart review, retrospective	13 patients	III	This research received no external funding. IRB approval was obtained from the Ethics Committee of the University Hospital of Messina. Informed consent was obtained from all subjects.		(+)
Di Zazzo et al., 2022[36]	Italy	Case series	3 patients	II, III	The authors received no financial support for the project. Informed written consent was obtained from the patients. Ethics committee approval was sought.	(+)	
Cheung et al., 2022[37]	United States	Chart review, retrospective	16 patients	II	No funding was received for this study.	(+)	
Arboleda et al., 2022[38]	United States	Cohort study, prospective	5 patients	I, II	Funded by Research to Prevent Blindness, National Eye Institute center grant P30-EY026877, and Dompé farmaceutici S.p.A. Registered at ClinicalTrials.gov at NCT04552730, obtained written informed consent before study initiation.	(+)	
Pieragostino et al., 2022[39]	Italy	Case series[a]	15 patients	II, III	Funding source not reported.		(+)
Habibi et al., 2021[40]	NR	Case series	2 patients	NR	Funding source not reported. IRB approval and informed consent not reported.	(+)	

(*continued*)

TABLE 2. (CONTINUED)

First author	Country	Study design	Sample size	NK Stage(s)	Funding	Data included	
						CS	CI
Hatcher et al., 2021[41]	United States	Case series[b]	8 patients, all younger than 18 years	I, II, III	Supported by an unrestricted Vanderbilt departmental award from Research to Prevent Blindness. One of the authors was a scientific advisor for Dompé.	(+)	
Zwingelberg et al., 2020[42]	Germany	Chart review, retrospective	11 patients	II, III	Authors assert no connections with a company whose product is named in the article or who makes a competitor product. One author was an advisor to Dompé.	(+)	
Pflugfelder et al., 2020[16]	United States	RCT, double-masked	48 patients	II, III	Supported by Dompé Farmaceutici SpA. Dompé participated in the design and conduct of the study; data collection for immunogenicity assessments; management, analysis, and interpretation of the data; and preparation and review of the article. The sponsor was not involved in efficacy data collection for masked central analysis. IRB approval was obtained. All participants provided informed consent.	(+)	
Mastropasqua et al., 2020[43]	Italy, United Kingdom	Case series[a]	18 patients	II, III	No government or nongovernment support was received for the conduct of this study. No financial disclosures were reported for any author. Written consent was obtained from all patients involved in the study. IRB approval was obtained by the Review Board of the G. d'Annunzio University of Chieti-Pescara.	(+)	(+)
Bonini et al., 2018[15]	Belgium, France, Germany, Hungary, Italy, Poland, Portugal, Spain, United Kingdom	RCT, phase 3	156 patients	II, III	Supported by Dompé Farmaceutici SpA. The sponsor participated in the design and conduct of the study; data collection for pharmacokinetics and immunogenicity assessments; management, analysis, and interpretation of the data; and preparation and review of the article. The sponsor was not involved in efficacy data collection for masked central analysis.	(+)	

(*continued*)

TABLE 2. (CONTINUED)

First author	Country	Study design	Sample size	NK Stage(s)	Funding	Data included	
						CS	CI
					The Institutional Review Board of Sapienza University of Rome and an independent ethics committee from each country with 1 or more participating sites approved the study, and informed consent to participate in the study was obtained from all patients.		

[a]Prospective case series.
[b]Retrospective case series.
CI, corneal innervation; CS, corneal sensation; NK, neurotrophic keratopathy; NR, not reported; RCT, randomized controlled trial; (+), data were included.

and corneal dystrophy (all $n < 10$ patients). Concomitant ocular therapies reported in the included studies were extracted where available and are summarized in Supplementary Table S1. The majority of studies (21/25) evaluated topical cenegermin applied six times daily for 8 weeks, although a few studies reported that some patients received a shorter treatment course (3/25 studies) or did not report the length of treatment (1/25 studies). Treatment duration and frequency were generally consistent, but follow-up duration varied significantly, from no follow-up after the 8-week treatment period to 2 studies that followed patients for 4 years after treatment.[25,31] Ten studies followed patients for the 8-week treatment course and 9 studies followed patients for more than a year (Supplementary Table S2). Because most studies reported outcomes at the 8-week treatment endpoint, pooled analyses of CS and CI primarily reflect short-term changes, and interpretation of longer term improvements should be made cautiously.

Corneal sensation

Of the 21 studies that reported data on CS, 19 provided results both pre- and post-cenegermin treatment. The majority of these studies (18/19) reported improvements in CS post-cenegermin. The remaining study, which was a case series of pediatric patients, reported that no patients experienced a documented improvement in CS, although the authors noted that assessment of CS was inconsistently documented among the patients.[41] To assess CS, 13 studies used CBE, 3 used a cotton-wisp test, 1 used nonminted dental tape, 3 used mixed methods (CBE in combination with non-CBE techniques), and 1 study did not report the CS assessment method. In the 9 studies reporting patient-level data, CS improved in 83.9% (146/174) of patients, with variability reflecting differences in baseline function and assessment methods (see Table 3).

Pooled analysis of CBE-reported CS

Of the 19 studies that provided CS results both pre- and post-cenegermin treatment, 8 were included in further analyses because they provided quantitative CBE data in the text or in tables. Improvements in CS following 8 weeks of treatment with cenegermin were consistently observed across these studies, with varying magnitude depending on baseline disease severity. Mean change in CS was greatest among patients with moderate-to-severe NK (stage II or III). A pooled analysis across all 8 studies showed a weighted mean CS increase from 1.76 cm at baseline to 3.81 cm post-cenegermin treatment, representing an improvement of 2.05 cm or 116.5% (see Table 4).

Corneal innervation

Of the 8 studies that reported data on CI, 6 provided results both pre- and post-cenegermin treatment. All 8 studies utilized *in vivo* confocal microscopy to assess parameters such as nerve fiber density, length, branching, or fractal dimension, although not every study reported on all variables. Regeneration rates ranged from 0.8 ± 0.5 mm/mm^2 to 1.87 mm/mm^2 per month in the 2 studies that reported corneal nerve regeneration rates. Improvement was seen across all studies, although the degree of improvement varied by study. Increases were reported in total, main, and branch nerve densities, with several studies reporting statistically significant gains as early as

Table 3. Studies Reporting Corneal Sensation Data

Article	*Sample size*	*NK stage(s)*	*Method (data type)*	*CS data*[a]
Hamrah et al., 2024[18]	37 patients	I	CBE (quantitative)	Improved corneal sensation (CS) in 91.2% patients (95% CI 76.3–98.1%; $P < 0.001$) at week 8, 82.1% patients (95% CI 63.1–93.9%; $P < 0.001$) at week 32. Mean CS increased from baseline (2.28 cm; SD, 1.27) to week 8 (4.12 cm; SD,1.61) and week 32 (4.16 cm; SD, 1.79).
Dai et al., 2024[23]	NR	I	NR	The authors observed that reported side effects from the second-round treatment were more severe compared with the first time, which they suggested could indicate possible increased CS.
Epitropoulos et al., 2022[30]	4 patients	I	Nonminted dental tape (qualitative)	3/4 patients had improved CS post-treatment. NR for the last patient.
Arboleda et al., 2022[38]	5 patients	II, II	CBE (quantitative)	CBE before treatment: 14.7 ± 6 mm (1.47 ± 0.6 cm). CBE after treatment: 26.7 ± 12 (2.67 ± 1.2 cm) ($P = 0.009$).
Qu et al., 2024[22]	9 patients	II, III	CBE (quantitative)	Central CS and the average CS of superior, inferior, nasal, and temporal quadrants increased significantly from baseline to 8- and 12-week follow-up ($P < 0.05$).
Bruscolini et al., 2022[25]	18 patients	II, III	CBE (quantitative)	Mean CS at baseline: 1.2 ± 1.3 cm Improvement after treatment at different follow-up periods: 12 months: 1.83 ± 0.84 cm ($P < 0.05$; 95% CI, 1.42–2.25 cm) 24 months: 1.86 ± 0.76 cm ($P < 0.05$; 95% CI, 1.48–2.24 cm) 36 months: 1.95 ± 0.83 cm ($P < 0.05$; 95% CI, 1.36–2.54 cm) 48 months: 2.11 ± 1.08 cm ($P < 0.05$; 95% CI, 1.28–2.94 cm)
Pedrotti et al., 2022[26]	18 patients	II, III	CBE (quantitative)	At baseline, CS was absent in the central corneal sector (the lesion site), while a low sensation was present in one or more sectors in 11 patients. CBE: increase in all corneal sectors at 8 weeks, 2 months, and 4 months of follow-up ($P \leq 0.01$); it improved further at the 8-month follow-up, except in the superior sector, where the median value of CBE was stable.
Roszkowska et al., 2022[29]	21 patients	II, III	CBE (quantitative)	Stage II: During total follow-up time [$x^2(2) = 11.565$, $P = 0.003$]; median IQR sensation level was: 1.5 cm (1–3.25) at baseline, 3.75 cm (2.4–5.3) at 4 weeks, and 4.5 cm (3.8–5.5) at 8 weeks. No statistically significant difference between 4 and 8 weeks of follow-up ($P = 0.063$). Increase at 4 and 8 weeks compared with baseline ($P = 0.031$, $P < 0.032$ respectively). Stage III: During total follow-up time [x^2 (2) = 22.37, $P <$ 0.001]; median IQR was: 1.5 cm (0.25–3.5) at baseline, 4 (3.5–4.75) at 4 weeks, and 4.5 cm (3.5–5.0) at 8 weeks. Increase in levels at baseline vs 4 weeks ($P = 0.001$), baseline vs 8 weeks $P = 0.001$, and 4 weeks vs 8 weeks ($P = 0.031$).
García-Delpech et al., 2022[31]	5 patients	II, III	CWT (qualitative)	At week 9, CS improvement was noted in all patients.
Bu et al., 2022[32]	4 patients	II, III	Non-CBE (qualitative), CBE (quantitative)	In 75% (3/4) of patients, sensation improved at cessation of therapy as measured by CBE. For the last patient, sensation improved slightly using qualitative measurement.
Meduri et al., 2022[33]	11 patients	II, III	CBE (quantitative)	Baseline: 1.6 ± 1.5 cm, 8 weeks: 4.25 ± 1.3 cm

(*continued*)

Table 3. (Continued)

Article	*Sample size*	*NK stage(s)*	*Method (data type)*	*CS data*[a]
Sacchetti et al., 2022[34]	24 patients in cenegermin group, 16 patients in AMT group	II, III	CWT (qualitative)	Only baseline data available (*N*) Cenegermin: hypoesthesia 9, anesthesia 15
Di Zazzo et al., 2022[36]	3 patients	II, III	CBE (quantitative)	Cases 1 and 2: Improved and returned within normal limits after complete healing of corneal ulcer Case 3: Improved from anesthesia to hypoesthesia.
Cheung et al., 2022[37]	14 eyes with both pre- and post-treatment data	II, III	CWT (qualitative)	Pretreatment CS present in 7% of eyes (1/14), mean of 0.1 quadrants (1/56) Post-treatment CS present in 79% of eyes (11/14) ($P < 0.0001$), mean of 1.6 quadrants (22/56, $P = 0.0005$)
Zwingelberg et al., 2020[42]	11 patients at baseline, 8 patients at 18 months	II, III	CBE (quantitative)	Baseline: 2.9 cm ± 1.9 cm (minimum 1/6, maximum 4/6) 18 months: 4.2 cm ± 1.7 cm (minimum 2/6, maximum 6/6) ($P = 0.015$)
Pflugfelder et al., 2020[16]	24 patients per group at baseline; 18 patients in cenegermin group and 15 patients in vehicle group at 8 weeks	II, III	CBE (quantitative)	CBE measures at baseline ($n = 24$), postbaseline by week 8 ($n = 18$) Cenegermin: baseline: 0.81 cm (SD, 1.187), week 8: 2.91 cm (SD, 2.144)
Mastropasqua et al., 2020[43]	NR, assume 18 patients	II, III	CBE (quantitative)	Median (IQR); baseline, 8 weeks Supertemporal: 2.0 cm (0.5–6.0), 3.0 cm (1.6–5.0), $P = 0.422$ Superonasal: 1.0 cm (1.0–5.0), 3.7 cm (2.6–5.5), $P = 0.028$ Inferotemporal: 0.5 cm (0–3.7), 3.0 cm (2.2–6.0), $P = 0.002$ Inferonasal: 0.5 cm (0–2.0), 4.0 cm (3.1–6.0), $P < 0.001$ Lesion: 0 cm (0–1.5), 3.5 cm (2.2–6.0), $P < 0.001$
Bonini et al., 2018[15]	42 patients on cenegermin 10 μg/mL, 42 patients on cenegermin 12 μg/mL, 38 patients in vehicle group	II, III	CBE (quantitative)	Number of patients with improvements in CS (%) at 8 weeks Cenegermin 10ug/ml: 33/42 (78.6%), $P = 0.303$ vs vehicle Cenegermin 20ug/ml: 29/38 (76.3%), $P = 0.442$ vs vehicle
Balbuena-Pareja et al., 2023[24]	NR, assume 25 patients	I, II, III	CBE (quantitative)	Median CS improved from 2.5 cm (range: 0.5–4.0) to 4.5 cm (range: 0.5–6.0) post-treatment ($P = 0.001$), with an improvement in sensation seen in 92.86% of patients with stage I NK.
Hatcher et al., 2021[41]	8 patients	I, II, III	CBE (quantitative), other (qualitative)	CS did not improve in any patients, although sensation was inconsistently documented in this study.
Habibi et al., 2021[40]	2 patients	NR	CBE (quantitative), other (qualitative)	Case 1: Pretreatment <0.5 cm (OD), <0.5 cm OS; post-treatment 2.5 cm OU; 3 months after therapy 0.5 cm OU. Case 2: Pretreatment markedly decreased sensation in OD, no sensation in OU; post-treatment NR; 1 month after therapy clinical signs and symptoms regressed.

[a]CS data were abstracted at the patient level unless otherwise noted in the table. Eye-level measurements (e.g., in studies reporting OD, OS, or OU separately) were averaged where possible; study-level weighted means reflect aggregated patient data rather than independent eyes.

AMT, amniotic membrane transplantation; CBE, Cochet–Bonnet esthesiometer; CWT, cotton wisp test; IQR, interquartile range; NK, neurotrophic keratopathy; NR, not reported; OD, right eye; OU, both eyes; OS, left eye; SD, standard deviation.

Table 4. Weighted Mean Analysis of Corneal Sensation Changes with Cenegermin

Article	*Sample size*	*CS, baseline*	*CS, week 8*	*Mean change*[a]	*Percent change*
Mild (stage I)					
Hamrah et al.[18]	37 patients	2.28 cm	4.12 cm	1.84 cm	80.7%
Mild/Moderate (stages I, II)					
Arboleda et al.[38]	5 patients	1.47 cm	2.67 cm	1.2 cm	81.6%
Bruscolini et al.[25]	18 patients	1.2 cm	2.95 cm	1.75 cm	145.8%
Moderate/Severe (stages II, III)					
Roszkowska et al.[29]	21 patients	1.81 cm[b]	4.43 cm[b]	2.62 cm	144.8%
Meduri et al.[33]	11 patients	1.6 cm	4.25 cm	2.65 cm	165.6%
Pflugfelder et al.[16]	24 patients[c]	0.81 cm	2.91 cm	2.1 cm	259.3%
Mastropasqua et al.[43]	18 patients[d]	1.85 cm	3.85 cm	2.0 cm	108.1%
Mild/Moderate/Severe (stages I, II, III)					
Balbuena-Pareja et al.[24]	25 patients[d]	2.3 cm[e,f]	4.1 cm[e,f]	1.8 cm	78.3%
Weighted mean for all included studies		1.76 cm	3.81 cm	2.05 cm	116.5%

[a]Weighted mean calculations and reported changes reflect study-level patient averages; eye-level data were not consistently reported and thus not able to be incorporated.
[b]In Roszkowska et al., separate values were provided for patients with moderate and severe disease; we calculated a single weighted mean using the reported sample sizes to maintain consistency with other studies.
[c]There were 24 patients at baseline and 18 patients at 8 weeks.
[d]An assumption about the number of patients was made based on the available data in the study.
[e]Mean change from baseline to week 8 was calculated using the Meta Converter calculator in studies that only reported the median and interquartile range (IQR).
[f]CS was reported as mean values for the superotemporal, superonasal, inferotemporal, and inferonasal quadrants, as well as the lesion. For consistency, a single mean was calculated by averaging these values together.
CI, corneal innervation; CS, corneal sensation.

8 weeks post-cenegermin treatment. In addition to density, structural parameters of nerve regeneration also improved. One study reported significant increases in corneal nerve fiber density (CNFD), particularly in peripheral corneal sectors, with progressive centripetal regrowth (see Table 5).[26]

Pooled analysis of CI improvements

Of the 6 studies that reported CI results both pre- and post-cenegermin treatment, only 3 provided nerve density data in the text or in tables in a way that could be used for quantitative synthesis. CNFD improved following 8 weeks of cenegermin treatment in all 3 studies, with the magnitude of change varying depending on baseline disease severity. When pooled across the 3 studies that met inclusion criteria—defined as reporting CNFD at 8 weeks using quantitative methods—the weighted mean CNFD increased from 3.1 mm/mm^2 at baseline to 5.1 mm/mm^2 at week 8. This corresponds to an absolute mean increase of 2.0 mm/mm^2, representing a 64.5% improvement from baseline. Cenegermin was shown to promote corneal nerve regeneration across varying disease severity (see Table 6).

ROB assessments

We evaluated ROB for each included study using the previously described NHLBI tools. Of the 25 studies, 8 were rated good, 12 fair, and 5 poor. Randomized controlled trials generally had lower ROB, while case–control studies showed higher risk compared with pre–post studies. Case series had mixed ratings, with most falling into the fair quality category.

Given the substantial heterogeneity in study design, outcome reporting, and sample sizes, as well as the limited number of studies contributing data to quantitative syntheses, it was not feasible to conduct formal weighting by ROB or sensitivity analyses to exclude lower quality studies. Instead, ROB assessments informed narrative interpretation and strength of conclusions, with greater caution applied to studies rated as fair or poor quality. The ROB assessments are presented in Supplementary Tables S3–S6.

Discussion

This systematic literature review and weighted analysis offer a comprehensive examination of cenegermin's effects on CS and CI in patients with NK. Across 25 published studies that met all the inclusion criteria, 21 studies reported on CS and 8 studies reported on CI. Both CS and CI showed improvement at 8 weeks post-treatment, which was the only time point that was reported quantitatively across all studies. A pooled analysis of CS found a mean improvement across 134 patients drawn from 8 studies of 2.05 cm (116.5%); studies that included more moderate and severe stage II and III patients demonstrated the greatest improvement in CS. A pooled analysis of CI data demonstrated a mean improvement of 2.0 mm/mm^2 (64.5%) in CNFD from baseline to 8 weeks post-treatment.

Although cenegermin's pivotal trials (NGF0212 [REPARO], NGF0214) were able to demonstrate its efficacy and safety, they were not able to determine statistically significant improvements in CS due to limitations on sample size and length of follow-up.[15,16] Subsequent independent studies have since demonstrated significant improvements in CS after treatment with cenegermin.[18,24,30–32,36–38,42] However, these studies were limited by small sample sizes, retrospective designs, and heterogenous populations, which limited their ability to extrapolate findings to a broader patient population. To address this evidence gap, we conducted a systematic literature review to analyze and synthesize the peer-reviewed literature on the impact of cenegermin on CS and CI. By focusing specifically on nerve-related

Table 5. Studies Reporting Corneal Innervation Data

Article	*Sample size*	*NK stage(s)*	*CNFD and length*[a]	*CN branch density*	*CN regeneration*
Balbuena-Pareja et al., 2023[24]	25 patients	I, II, III	Post-treatment, median total, main, and branch nerve densities in NK group were significantly lower than controls (all $P < 0.0001$). Compared with pretreatment values in NK, median post-treatment total nerve number in n/mm^2 increased [20.6 (range: 0.0–105.0), $P = 0.0118$] and main nerve number increased [8.1 (range: 0.0–38.8), $P = 0.0162$].	Post-treatment, branch nerve densities in NK group were significantly lower than controls (all $P < 0.0001$). Compared with pretreatment values in NK, branch nerve number increased [13.8 (range: 0.0–82.5), 0.0256].	Rate of nerve regeneration: 0.8 ± 0.5 mm/mm^2 per month.
Pedrotti et al., 2022[26]	18 patients	II, III	Quantitative analysis of the sub-basal nerves imaged with ACC metrics showed a significant increase in CNFD in all corneal sectors between each contiguous time interval until the 4-month follow-up ($P < 0.05$). At 8-month follow-up, the CNFD progressively increased in all corneal sectors, except in the central one, which decreased due to the two relapsed patients. Progressive nerve regrowth was accompanied by a gradual increase in branching over time.	A significant increase in CNBD was observed in the superior ($P = 0.05$) and temporal ($P = 0.01$) sectors from 8 weeks, in the nasal sector ($P = 0.01$) from the 2-month follow-up and in the inferior one ($P = 0.04$) from the fourth month. Although no significant branching was detectable in the central corneal sector until the last follow-up, the growing trend of the IQR indicated initial branching also in the central cornea in some patients.	There was centripetal progression of sub-basal corneal nerve regrowth, especially in the peripheral cornea.
Saricay et al., 2022[27]	5 patients	I	At 8 weeks, mean total nerve density and main trunk nerve density increased ($P = 0.006$, $P = 0.013$, respectively; compared with baseline). Total nerve density (mean ± SD) Baseline: 3,356.52 ± 1,444.75 Post-treatment: 7,7518.69 ± 1,744.4[b] Main Trunk Nerve Density Baseline: 1,897.85 ± 875.03 Post-treatment: 4,045 ± 981.79	At 8 weeks, the branch nerve density increased ($P = 0.004$, respectively, compared with baseline. Branch nerve density Baseline: 1,454.51 ± 759.35 Post-treatment: 2,195.34 ± 856.64	The average speed of nerve regeneration was calculated as 1.87 mm/mm2 per month.
Inferrera et al., 2022[35]	3 patients at baseline, 5 patients completed follow-up	III	Baseline: Total absence of nerves (3/3 eyes). 8 weeks: In 4/5 eyes, sporadic fibers were detected.	NR	NR

(*continued*)

Table 5. (Continued)

Article	*Sample size*	*NK stage(s)*	*CNFD and length*[a]	*CN branch density*	*CN regeneration*
Pieragostino et al., 2022[39]	15 patients at baseline, 8 completed follow-up	II, III	The length, density, and number of ramifications of nerve fibers increase after 4 weeks of treatment (P-value <0.05) and after 8 weeks of treatment (P-value <0.01). The increased number of nerve fibers with respect to naïve ones is in accordance with the high number of neuronal CD171 + EVs. Nerve fiber diameter increased after 8 weeks ($P < 0.01$).	NR	NR
Mastropasqua et al., 2020[43]	NR, assume 18 patients	II, III	NK group: the sub-basal nerve fiber density increased significantly at week 4 and week 8. The mean density of nerve fibers was significantly higher at week 4 and week 8 in comparison to baseline.	The number of nerve branches and the diameter of nerve fibers increased significantly after 4 weeks of treatment.	A nerve regeneration rate of 1,079.129 ± 835 μm/mm^2 at 4 weeks and 661.898 ± 835 μm/mm^2 at 8 weeks was reported.

*All studies used IVCM.

[a]CNFD and related measures were abstracted at the patient or study level, as individual eye-level linkage was not consistently reported; table values may represent averages across eyes within a patient when possible.

[b]Possible data error, as reported in the article.

AS-OCT, anterior segment optical coherence tomography; CI, corneal innervation; CNFD, corneal nerve fiber density; CNFraD, corneal nerve fiber fractal dimension; CNBD, corneal nerve fiber branch density; DC, dendritic cell; EV, extracellular vesicles; HRT, Heidelberg retina tomograph; IVCM, *in vivo* confocal microscopy; NK, neurotrophic keratopathy.

Table 6. Weighted Mean Analysis of Corneal Nerve Fiber Density Changes with Cenegermin

Article	*Sample size*	*CNFD, baseline*	*CNFD, week 8*	*Mean change*[a]	*Percent change*
Saricay et al.[27]	5 patients	3.4 mm/mm^2[2a]	7.8 mm/mm^2[2b]	4.4 mm/mm^2	129.4%
Mastropasqua et al.[43]	18 patients	0.9 mm/mm^2[2b,c]	2.6 mm/mm^2[2b,c]	1.7 mm/mm^2	188.9%
Balbuena-Pareja et al.[24]	25 patients	4.6 mm/mm^2	6.4 mm/mm^2	1.8 mm/mm^2	39.1%
Weighted mean for all included studies		3.1 mm/mm^2	5.1 mm/mm^2	2.0 mm/mm^2	64.5%

[a]Weighted mean CNFD values reflect aggregated study-level patient averages; individual eye-level data were not consistently available.
[b]μm/mm^2 (micrometers per square millimeter) was converted to mm/mm^2 (millimeters per square millimeter).
[c]Mean was calculated from median, IQR, and sample size using the Meta Converter calculator.
CNFD, corneal nerve fiber density; IQR, interquartile range.

outcomes and standardizing measures of CS and CI, this review provides additional support that cenegermin is associated with meaningful improvements in CS during the initial 8 weeks post-treatment, while also enabling comparison between real-world studies.

Across the 21 articles reporting on CS that included quantitative data, the majority reported that cenegermin consistently improved CS from baseline to 8 weeks post-treatment, with an overall weighted mean percent change of 116.5% (range: 78.3%–259.3%) across all NK stages. Improvements were consistently observed across all stages of disease severity, and patients with more advanced NK at baseline trended toward greater CS improvements. This finding may reflect a larger capacity for improvement when starting with severe disease, compared with mild disease, where a measurement ceiling may limit detectable changes. However, the CBE is both examiner- and subject-dependent, introducing variability and potentially obscuring subtle improvements in milder cases. More refined and reproducible methods of CS measurement may better capture the true extent of treatment-related improvements in the future.

CI outcomes were less commonly reported, with only 6 studies providing post-treatment nerve fiber density data. Of these 6 studies, only 3 reported quantitative post-treatment CNFD values suitable for weighted analysis. Across these 3 studies, cenegermin was associated with corneal nerve regeneration, showing an average 2.0 mm/mm^2 increase in CNFD and a weighted mean percent change of 64.5% from baseline to 8 weeks post-treatment. Although comparison across studies was challenging due to diverse methodology, 6 studies reported improvement in nerve fiber density, nerve fiber length, or diameter following treatment with cenegermin.[24,26,27,35,39,43]

The observed CI improvements lend additional support to cenegermin's proposed mechanisms of action, which include promoting nerve regeneration, enhancing corneal epithelial healing, and restoring trophic support to damaged corneal tissue. The reported increases in CNFD align with preclinical data showing that cenegermin stimulates corneal nerve regeneration.[24,26,43] Although the average increase of 2.0 mm/mm^2 CNFD observed in our included studies seems low, it is possible that additional benefit could have been seen beyond 8 weeks post-treatment, a time point chosen as it was the only comparable follow-up length reported consistently across articles with quantitative data. For comparison, a small retrospective case series of 4 patients with severe NK treated with autologous serum tear drops demonstrated that corneal nerve density continued to increase over longer follow-up periods (from 0 to 10.09 ± 2.54 mm/mm^2 over 4–22 months), suggesting that nerve regeneration may extend well beyond the 8-week time point reported here.[44] One study observed recovery of sub-basal corneal nerves in patients treated with cenegermin, beginning at 8 weeks and continuing through 8 months post-treatment.[26] Significant regrowth was noted in corneal nerve fiber length from 8 weeks onward and in CNFD starting at 2 months, with both measures showing continued improvement throughout follow-up.[26] Our CS and CI findings reinforce the idea that cenegermin acts as a disease-modifying therapy for NK, not only promoting epithelial healing but also contributing to restoration of CS across all NK stages. Improvements in CI are particularly significant because of the central role corneal nerves play in maintaining ocular surface health, tear production, and epithelial turnover. It is encouraging that substantial CS gains were seen even in patients with severe disease, a group that is at significant risk of corneal perforation and vision loss.[45] As a key measure of corneal health, the increase in CS observed in this review provides additional evidence that cenegermin improves corneal nerve function. Importantly, however, CI and CS are not always well correlated, and the magnitude of improvement in one does not necessarily predict the other. Future studies would benefit from evaluating whether there are critical thresholds of CI and CS recovery that correspond to clinically meaningful improvement, which could better define treatment success with cenegermin.

This study had several limitations. The included articles were heterogenous in design, patient populations, and outcomes measures, with findings influenced by uncontrolled case series, thereby limiting the strength of causal inference. Both pediatric and adult patients were included, despite known differences in baseline corneal physiology and nerve regeneration capacity, because cenegermin is approved in the United States for patients older than 2 years and available real-world evidence frequently reports outcomes across broad age ranges without stratification.

The use of concomitant topical or systemic ocular therapies alongside cenegermin was inconsistently documented and could not be systematically adjusted for, raising the possibility of confounding by other treatments (e.g., autologous serum, antibiotics). Importantly, in many studies, cenegermin was initiated in patients who were refractory or had an inadequate response to these same therapies prior to cenegermin treatment. Therefore, while residual confounding from concurrent treatments cannot be entirely excluded, the observed clinical improvements following cenegermin initiation are unlikely to be primarily attributable to these concomitant interventions. Ocular comorbidities that could impact corneal nerve health or healing (e.g., dry eye disease, prior corneal grafts, or previous ocular surgeries) were inconsistently reported across studies and could not be incorporated into our analysis. Underlying etiology (e.g., herpetic, postsurgical, diabetic) may also

influence the regenerative potential, but we did not conduct subgroup analyses because most of the studies did not provide patient- or eye-level linkage between specific outcomes and etiologies. Because patient- and eye-level linkage was not consistently reported, analyses were conducted at the study level, and weighted means reflect aggregated study-level data rather than individual eyes. Consequently, we were unable to account for within-patient correlations in these analyses.

Although all studies followed patients through the 8-week treatment course, follow-up beyond 8 weeks varied considerably, limiting comparisons of longer term outcomes. Weighted means could only be calculated for studies reporting quantitative CS or CI data; studies reporting aggregated or incomplete results restricted our ability to conduct subgroup analyses by disease stage or measurement methodology. Furthermore, studies reported CS outcomes as pooled across heterogeneous assessment techniques without standardization, which could introduce measurement bias.

Finally, the literature search was restricted to English-language publications following cenegermin's US FDA approval in August 2018, excluding studies published after its EMA approval in July 2017. Data extraction was performed by a single reviewer and verified by a second. Lastly, while efforts were made to minimize overlapping patient populations, duplication cannot be entirely excluded in studies with few patients, given the rarity of NK and patient confidentiality.

Conclusions

Cenegermin treatment is associated with both structural and functional improvements in CI and CS across the spectrum of NK severity, highlighting the regenerative potential of cenegermin in patients with NK. Future research with larger and more diverse patient populations conducted with standardized quantitative methods to measure CS and CI would help establish the long-term efficacy of corneal neuronal recovery induced by cenegermin.

Authors' Contributions

S.S.M.F.: Conceptualization, supervision, and writing—review and editing. C.C.: Conceptualization, formal analysis, methodology, project administration, and writing—review and editing. J.W.: Formal analysis, methodology, project administration, writing—original draft and preparation, and review and editing. I.Y.: Conceptualization, formal analysis, funding acquisition, methodology, project administration, supervision, and writing—review and editing.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
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Supplementary Table S5
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