Progressive GCIPL thinning developed outside the elliptical annulus would, thus, be missed by the current GCIPL analysis, which may account for the seemingly lack of spatial correspondence between progressive RNFL thinning and progressive GCIPL thinning over the inferior retina in the case example shown in Figure 1A. The superotemporal RNFL defects, as well as the superotemporal GCIPL defects albeit less obvious, were evident in the RNFL thickness map and the GCIPL thickness map, respectively, at the baseline visit. A more precise and meaningful assessment of spatial correspondence would have been feasible had a larger scan area of the macula for GCIPL thickness analysis been available. Likewise, it is difficult to decipher whether the progressive RNFL thinning and progressive GCIPL thinning over the inferior retina in the case example shown in Figure 1B correspond with the same location without a widefield scan.

Rather than focusing on the spatial correspondence, the key message of our study is that integrating both the optic disc region and the macula is pertinent to improving the detection of optic nerve degeneration in glaucoma because progressive RNFL thinning over the optic nerve head region and progressive GCIPL thinning over the macula are mutually predictive, and they are both indicative of subsequent development of visual field loss. Widefield RNFL/GCIPL progression analysis would be transformative for early detection of disease deterioration in glaucoma patients.

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Re: Bonini et al.: Phase 2 randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis (*Ophthalmology*. 2018;125:1332-1343)

TO THE EDITOR: I read with great interest the REPARO study by Bonini et al[1] on the use of topical *Escherichia coli*-derived recombinant human nerve growth factor (rhNGF) in treating stage 2 to 3 neurotrophic keratitis (NK). As highlighted by the authors, NK is a rare yet challenging and potentially sight-threatening clinical condition with a high unmet need for treatment. Currently, the majority of treatment aims to support corneal healing and very few therapeutic approaches, including topical NGF and corneal neurotization surgery, address or restore the underlying corneal anesthesia.[2]

There are several aspects in which I feel that they could benefit from further clarification. First, the authors demonstrated a significantly higher rate of corneal healing in patients who received topical rhNGF 10 μg/ml and rhNGF 20 μg/ml compared with those who received vehicle treatment at the 8-week time point. However, despite a similar rate of improvement in corneal healing between both rhNGF groups, only the rhNGF 10 μg/ml group attained a significant visual improvement in terms of least squares mean change from baseline to week 8. It would be useful if the authors could clarify whether the visual improvement was attributed to the difference in the severity of NK, where there were more stage 3 NK in the rhNGF 10 μg/ml group than in the rhNGF 20 μg/ml group (although not statistically significant), and whether there was any difference in the pretreatment visual acuity between the 2 groups, which could affect the magnitude of improvement after treatment.

Second, it is interesting to note that corneal sensation improved more significantly in patients who received topical rhNGF of lower concentration (10 μg/ml) than those who received rhNGF of higher concentration (20 mg/ml). It would be useful if the authors could provide further information on the baseline level of corneal anesthesia and the duration of denervation, which could be important confounding factors, between the 2 groups and to comment on whether in vivo confocal microscopy was performed to quantify and qualify nerve regeneration. Studies have shown that the regenerative capacity of denervated peripheral nerves diminishes over time.[3] Our study on corneal neurotization surgery for 2 patients with stage 3 NK after removal of cerebellopontine angle meningioma demonstrated that the corneal sensation of one patient, with a denervation time of 3.7 years, improved significantly from 0 to 60 mm after the surgery, whereas the corneal sensation of the other patient, with a denervation time of 13.6 years, only improved transiently from 0 to 5 mm at 15 months postoperatively, and returned back to 0 mm at 2 years postoperatively, suggesting a possible prognostic effect of denervation time on the success of restoration of corneal sensation.[4] However, such association was not consistently observed by Terzis et al,[5] highlighting the complexity of the corneal homeostasis and regeneration of corneal nerves.

Third, it would be useful if the authors could comment on any common risk factors or characteristics, including the demographic factors, underlying causes, severity of corneal anesthesia, and denervation time, in patients whose corneal sensation did not improve in the REPARO study. Knowledge of these factors may provide useful prognosticating values when it comes to selecting and counselling patients with moderate to severe NK for topical NGF treatment and planning a phase 3 trial in the future.

Last, the recurrence rate of the NK, defined by recurrent persistent epithelial defect or corneal ulcer, was very low across all groups. It would be beneficial if the authors could comment on whether the improvement of corneal sensation was sustained at the final follow-up, which might explain the low recurrence rate in the rhNGF treatment groups or whether the success of initial treatment

was sufficient to restore the homeostasis of corneal epithelium. Interestingly, the vehicle treatment group similarly achieved a low recurrence rate. Having some information on the maintenance treatment during the 48-week follow-up period, especially whether the treatment regimen was similar across all groups, would also be useful for the readers.

This REPARO trial represents a giant leap forward in the field of NK, with promising efficacy and safety of topical rhNGF being demonstrated via an international collaborative effort. The adoption of topical NGF as part of the therapeutic armamentarium of NK in clinical practice will hopefully become a reality once more robust evidence is generated from further phase 3 clinical trials in the near future.

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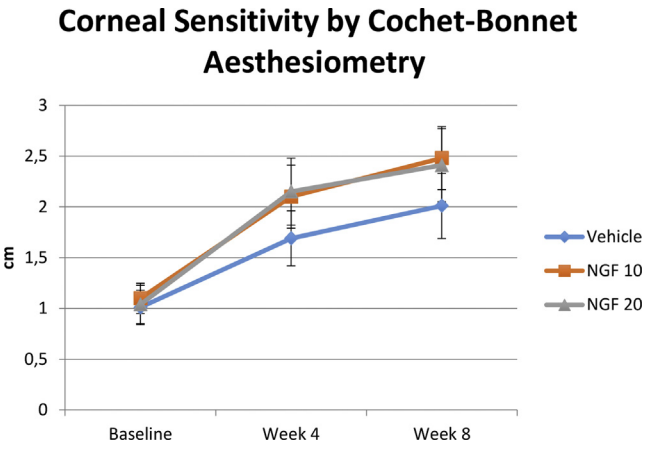

Figure 1. Increase in corneal sensitivity from baseline (a secondary endpoint in the REPARO clinical trial).

REPLY: We thank Dr Ting for raising this interesting discussion about some of the secondary endpoints of the REPARO clinical trial,[1] such as corneal sensation and visual acuity (best-corrected distance visual acuity). As a premise, it is important to underline that, although the REPARO Phase 2 clinical trial represents—with its 156 patients enrolled—the largest randomized controlled study ever conducted in neurotrophic keratitis (NK), the sample size was calculated only on the primary efficacy endpoint, corneal healing. Owing to the rarity of the condition, it would have been unfeasible to have a sample size sufficient to detect a statistically significant difference for other clinically relevant endpoints, such as corneal sensation and best-corrected distance visual acuity. However, with just 8 weeks of treatment, the recombinant human nerve growth factor (rhNGF)-treated groups showed a trend toward better efficacy in these endpoints compared with the vehicle control group, which could be clinically relevant, albeit not statistically significant.

Regarding the specific requests of clarification made by Dr Ting, we are pleased to provide more details that were omitted from the publication.

The groups were considered homogeneous in terms of disease severity at baseline (no significant difference in the number of patients with stage 2 or 3 NK); however, there was a slightly better best-corrected distance visual acuity score in the rhNGF 10 μg/ml group (31±28) compared with the rhNGF 20 μg/ml group (24±26). This finding may in part be responsible for the (not significant) difference in the magnitude of improvement after treatment. However, we suggest that no conclusions about relative efficacy should be drawn because a transient reduction in visual acuity may be a sign of epithelium regrowth over corneal wounds. This mechanism is crucial to allow persistent healing of a NK lesion, but until the reepithelialization process is complete, the growing epithelium can transiently alter corneal transparency.

Regarding corneal sensitivity, we did not observe that it improved more significantly in patients who received rhNGF 10 μg/ml compared with 20 μg/ml. In fact, there was no difference in the rhNGF groups at baseline and at any timepoint during treatment, and only at 1 timepoint (week 6) the rhNGF 10 μg/ml group reached statistical significance versus the vehicle control group. There was, however, a trend toward improvement that was almost identical in the 2 rhNGF groups and constantly greater than that observed in the vehicle control group (Fig 1). In contrast, it is interesting to note that, for patients who achieved complete corneal healing at the end of treatment, 86% in the rhNGF 10 μg/ml group and 100% in the rhNGF 20 μg/ml group showed further improvement or no change in corneal sensitivity at the end of the 1-year follow-up.

We agree with Dr Ting that it would be interesting to follow NK patients treated with rhNGF by in vivo corneal confocal microscopy. However, this examination was optional in the clinical study and only a few sites performed it in some patients. Therefore,