Phase IV Multicenter, Prospective, Open-Label Clinical Trial of Cenegermin (rhNGF) for Stage 1 Neurotrophic Keratopathy (DEFENDO)

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SUPPLEMENTARY MATERIAL

Supplementary Methods. Inclusion and exclusion criteria for NGF0120 phase IV trial.

Inclusion criteria for NGF0120 phase IV trial

Patients were eligible for study participation if they met the following criteria:

1. Male or female aged ≥18 years.

2. Patients with stage 1 neurotrophic keratopathy (NK) defined by the Mackie criteria.

3. Patients with stage 1 NK characterized by all the following:

a. Superficial punctate keratopathy (SPK) as shown by fluorescein corneal staining equal to a grade 3 within the central zone using the National Eye Institute (NEI) scale (Figure S5)

AND

b. Evidence of decreased corneal sensitivity (≤4 cm using the Cochet-Bonnet esthesiometer) in the central qualifying zone.

4. No improvement in NEI zone score between screening (visit 1) and baseline (visit 2) for the qualifying zone determined at visit 2.

5. A best-corrected distance visual acuity (BCDVA), using corrective lenses, if necessary, in the study eye of at least +1.0 logarithm of the minimum angle of resolution (logMAR; Snellen <20/200) if the investigator attributed the vision loss to the epithelium and the loss was not related to the macula in the affected eye(s).

6. The same eye (eligible eye/study eye) fulfilled all the above criteria at both screening (visit 1) and baseline (visit 2).

7. Patients with punctal occlusion or punctal plugs inserted prior to the study were eligible for enrollment provided that the punctal occlusion was maintained during the study period. If a punctal plug fell out during the study, it had to be reinserted within 7 days.

8. Patients at high risk of progression or with a history of stage 2 or stage 3 NK per the Mackie classification.

9. Patients who had only 1 functional eye could be included if they met all the criteria above and, per the investigator's discretion, were proper candidates to designate the 1 functional eye as the study eye.

10. Only patients who satisfied all informed consent requirements were included in the study. The patient and/or the patient's legal representative read, signed, and dated the institutional review board–approved informed consent document before any study-related procedures were performed.

11. Patients had the ability and willingness to comply with study procedures.

Exclusion criteria for NGF0120 phase IV trial

Patients were not eligible for study participation if they met any of the following criteria:

1. In the opinion of the investigator, there was evidence of an active ocular infection (bacterial, viral, protozoal) in either eye.

2. Patient used nondiagnostic (eg, topical drops used for clinical testing/evaluations) medications that could have induced corneal toxicity between screening (visit 1) and baseline (visit 2).

3. In the opinion of the investigator, patient had current conditions or a history of conditions that may have confounded the study data, including but not limited to ocular cicatricial pemphigoid, graft-versus-host disease, neuromyelitis optica, uncontrolled dry eye, and Stevens-Johnson syndrome.

4. Patient had a history of severe systemic allergy or severe ocular allergy (including seasonal conjunctivitis expected during the patient's participation in the trial) or chronic conjunctivitis and/or keratitis other than dry eye disease.

5. Intraocular inflammation, defined as Tyndall score >0.

6. Patient had severe vision loss with no potential for visual improvement in the study eye, in the opinion of the investigator, or if the patient was deemed legally blind.

7. Patient had active severe blepharitis and/or severe meibomian gland disease (MGD) who, in the opinion of the investigator, would require routine treatment during the study or had required routine treatment within 2 weeks of baseline (visit 2). This included the use of doxycycline within 2 weeks prior to visit 2 for active MGD.

8. Patient had a history of any ocular surgery (including eyelid surgery and cataract surgery) within the 3 months before baseline (visit 2), or laser-assisted in situ keratomileusis (LASIK) or refractive surgical procedures within 3 months before baseline (visit 2). An exception was allowed if, in the opinion of the investigator, the ocular surgery was deemed the cause of the NK.

9. Ocular surgery or elective ocular surgery was expected during participation in the trial.

10. Patient had prior surgical procedure(s) for the treatment of NK, including but not limited to tarsorrhaphy and conjunctival flap; an exception was made for amniotic membrane transplantation. Enrollment of patients previously treated with amniotic membrane transplantation was allowed 2 weeks after the membrane had fully disappeared within the area, with removal of any sutures or the Prokera ring at least 2 weeks before baseline (visit 2).

11. Patient had treatment with Botox (botulinum toxin) injections in the study eye, used to induce pharmacologic blepharoptosis, within 60 days prior to baseline (visit 2).

12. Patient had an anticipated need to use therapeutic contact lenses or contact lens wear for refractive correction in the study eye during the study treatment period.

13. Patient had an unstable medical condition that may have confounded the study data, in the opinion of the investigator, including but not limited to diabetes, thyroid disease, autoimmune disease, Parkinson’s disease, and multiple sclerosis. Stable conditions managed with oral or injectable medications were allowed if, per the investigator’s discretion, the patient was not anticipated to have flare-ups that would affect the ocular surface.

14. Patient had an eyelid abnormality that could alter eyelid function, including but not limited to blepharospasm, cerebrovascular accident, entropion, ectropion, and floppy lid syndrome.

15. Patient used glaucoma drops within 14 days prior to baseline (visit 2). Patients could use oral acetazolamide during the study to control intraocular pressure.

16. Patient was pregnant or lactating at study entry or planning a pregnancy.

17. Patient was a premenopausal female not using a medically acceptable form of birth control (abstinence, oral contraception, intrauterine device, surgically sterilized).

18. Patient had a history of drug addiction or alcohol abuse documented within the past 5 years.

19. Patient had participated in a clinical trial with a new active substance during the 14 days prior to baseline (visit 2). If a patient participated in another clinical trial for an ocular surface product beyond 14 days, the investigator evaluated prior to treatment that the product did not have residual effects on the ocular surface that could confound the data by having an effect on staining.

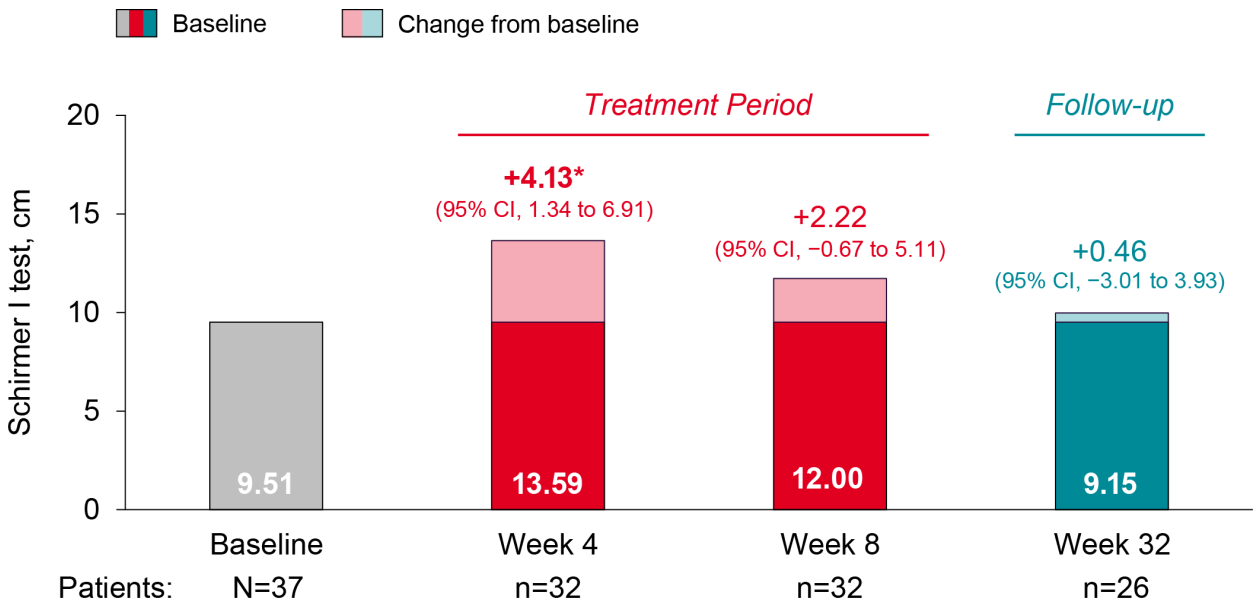
20. Patient was participating in another clinical trial study at the same time as the DEFENDO study.

21. Patient participated in an NK study during the 60 days prior to baseline (visit 2).

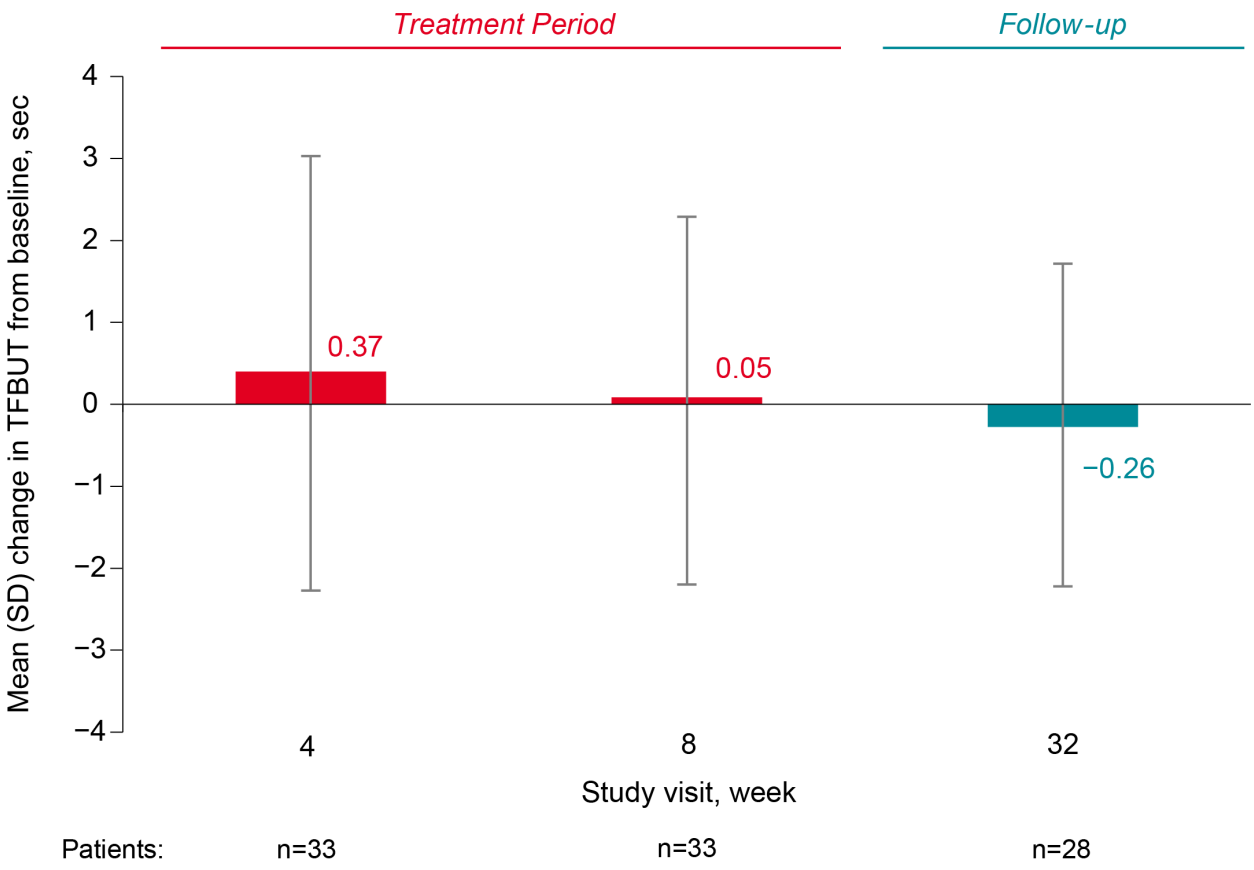
22. Patient was an employee of a site that was directly involved in the management, administration, or support of the DEFENDO study, or an immediate family member of the same.

23. Prior treatment for stage 1, 2, or 3 NK with 20 mcg/mL cenegermin ophthalmic solution had failed. Failure was defined as nonresponder or lack of efficacy.

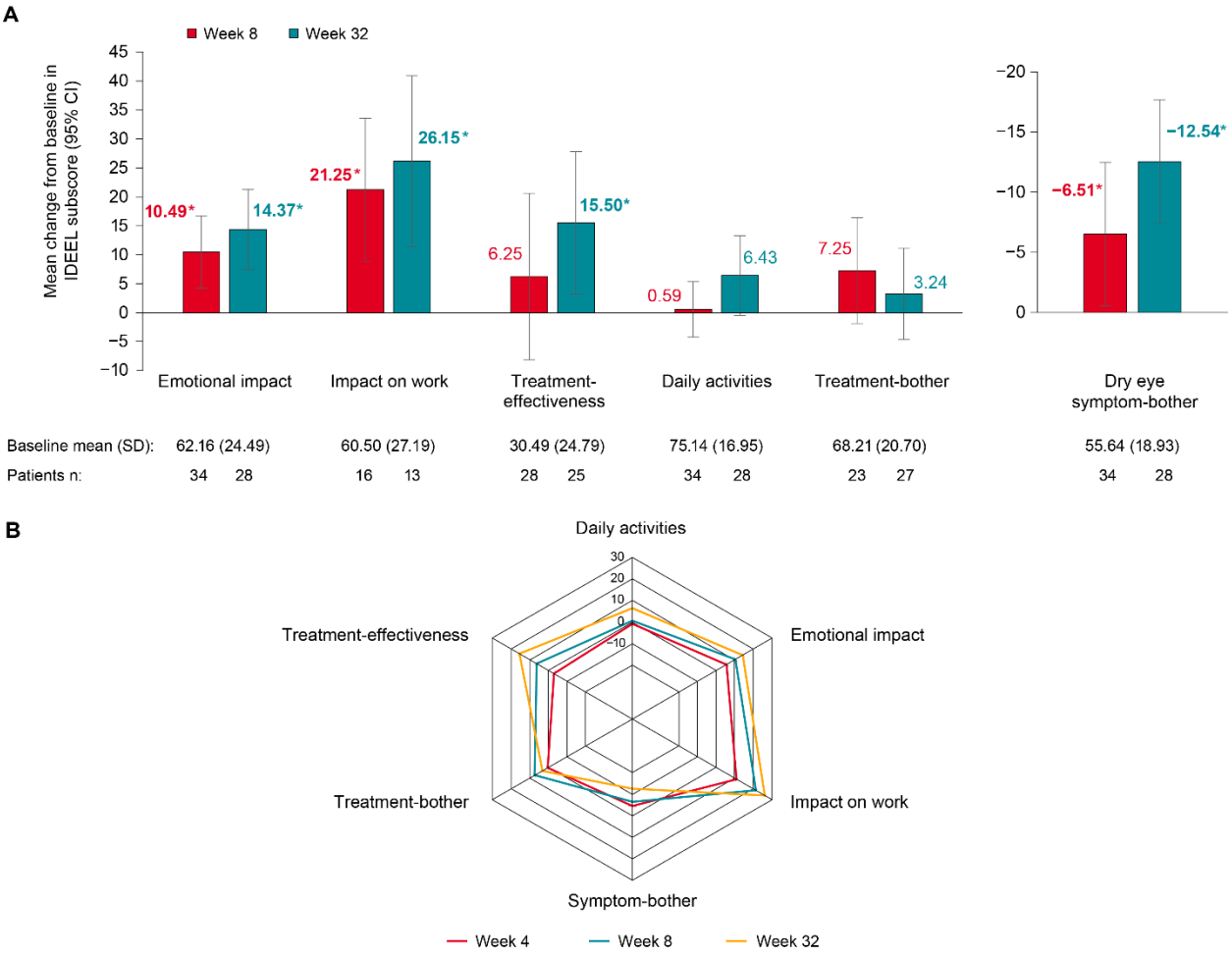
Supplementary Figure S1. Mean change from baseline to Week 32 in Schirmer I test. Lower bars indicate the baseline value and upper, lightly shaded bars represent change from baseline. Analyses were conducted for patients in the full analysis set with available data. CI, confidence interval. *Bold value denotes statistically meaningful change: *P*<0.05 (2-sided), based on evaluation of 95% CI. 95% CI based on Clopper-Pearson exact method.



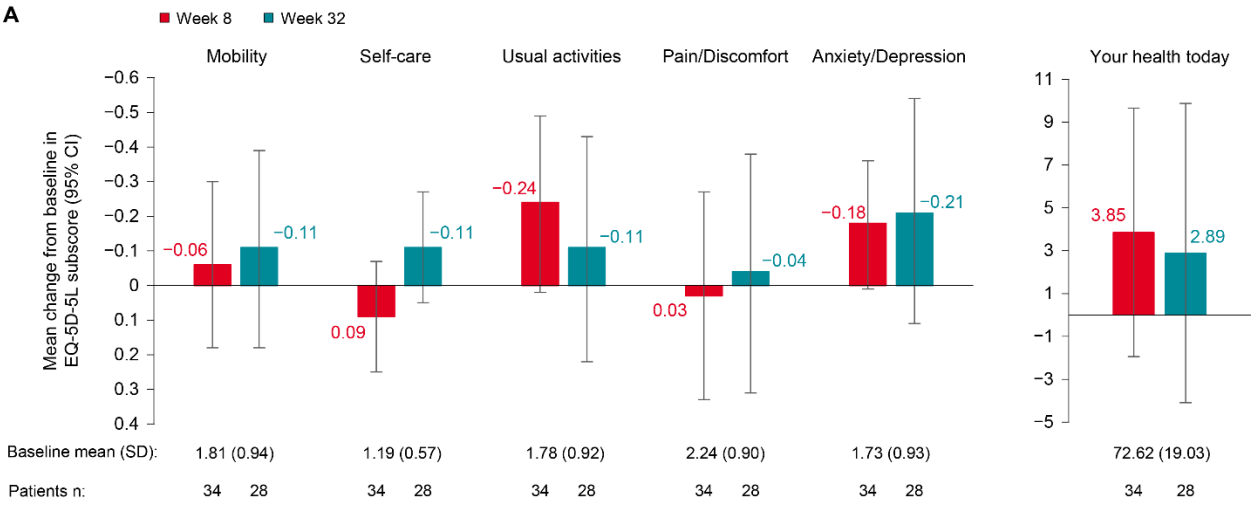
Supplementary Figure S2. Mean change from baseline in TFBUT assessed by an average of 2 repeated measurements. Mean baseline value was 4.3 (SD, 2.6) seconds. Analyses were conducted for patients in the full analysis set with available data. CI, confidence interval; SD, standard deviation; TFBUT, tear film breakup time. All *P*≥0.05 (2-sided), based on evaluation of 95% CIs. 95% CI based on Clopper-Pearson exact method.

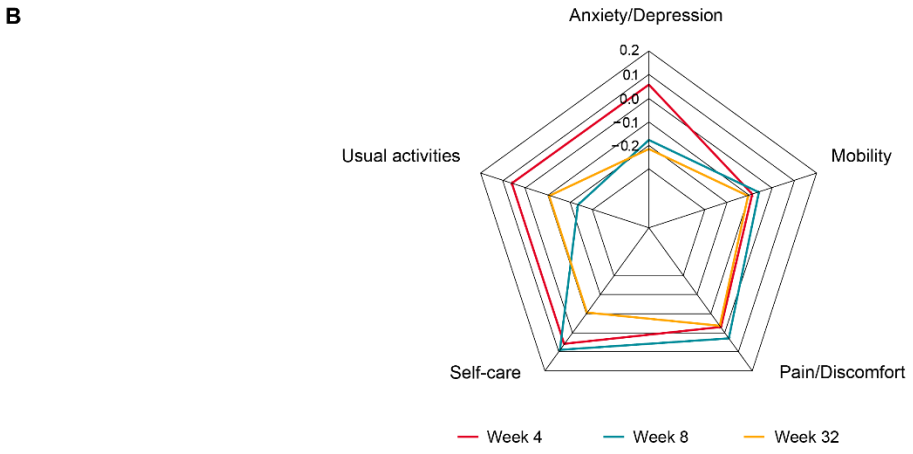


Supplementary Figure S3. Summary of quality-of-life outcomes as measured by IDEEL. **(A)** Mean change from baseline to Week 8 and Week 32 in IDEEL subscores. **(B)** Overall mean change from baseline to Week 32 in IDEEL subscores. Higher scores in treatment-effectiveness, emotional impact, treatment-bother, daily activities, and impact on work indicate improvement, whereas lower scores in symptom-bother indicate improvement (scores range from 0 to 100). Analyses were conducted for patients in the full analysis set with available data. CI, confidence interval; IDEEL, Impact of Dry Eye on Everyday Life; SD, standard deviation. *Bold value denotes statistically meaningful change: *P*<0.05 (2-sided), based on evaluation of 95% CI. 95% CI based on Clopper-Pearson exact method.

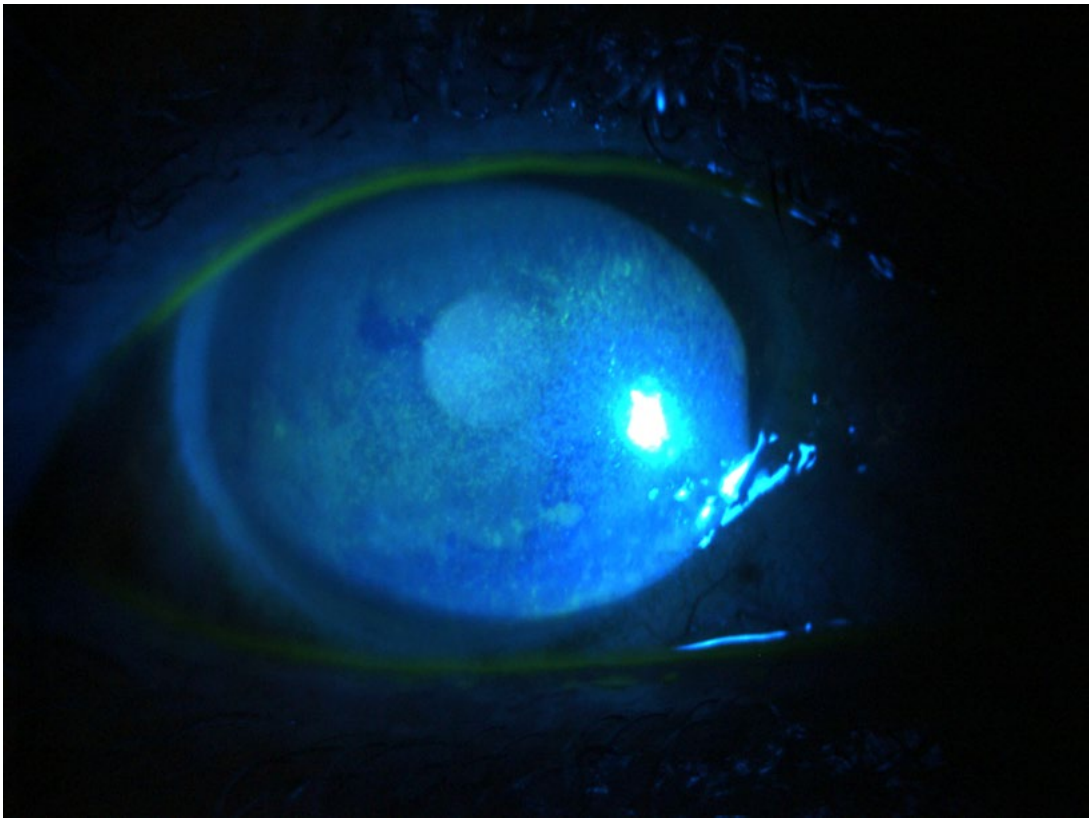


Supplementary Figure S4. Summary of quality-of-life outcomes as measured by EQ-5D-5L. **(A)** Mean change from baseline to Week 8 and Week 32 in EQ-5D-5L dimensions. **(B)** Overall mean change from baseline in EQ-5D-5L dimensions from baseline to Week 32. For EQ-5D-5L, lower scores indicate improvement across all subscales (scores range from 1 to 5). Analyses were conducted for patients in the full analysis set with available data. CI, confidence interval; EQ-5D-5L, EuroQoL 5-dimension 5-level; SD, standard deviation. All *P*≥0.05 (2-sided), based on evaluation of 95% CI. 95% CI based on Clopper-Pearson exact method.





Supplementary Figure S5. Representative image of patient with stage 1 NK with eligible inclusion criteria. Representative image of an eye with superficial punctate keratopathy as shown by fluorescein corneal staining equal to a grade 3 within the central zone using the National Eye Institute scale. NK, neurotrophic keratopathy.



Supplementary Table S1. Summary of Common (>10% of Patients) Ocular Medical Histories at Baseline

Parameters, n (%)	N=37
Any ocular condition	**36 (97.3)**
Eye disorders	**32 (86.5)**
Dry eye	21 (56.8)
Cataract	12 (32.4)
Neurotrophic keratopathy	10 (27.0)
Blepharitis	8 (21.6)
Cataract nuclear	6 (16.2)
Keratitis	4 (10.8)
Glaucoma	4 (10.8)
Punctate keratitis	4 (10.8)
Infections and infestations	**16 (43.2)**
Ophthalmic herpes zoster	8 (21.6)
Ophthalmic herpes simplex	4 (10.8)
Surgical and medical procedures	**30 (81.1)**
Intraocular lens implant	19 (51.4)
Cataract operation	14 (37.8)
Punctal plug insertion	5 (13.5)
Keratomileusis	4 (10.8)

Patients reporting more than 1 event are only counted once. Conditions were coded according to the Medical Dictionary for Regulatory Activities version 23.0.

Supplementary Table S2. Change From Baseline in IDEEL Questionnaire Subscores

	Study visit, week			
Subscore, mean (SD)	**Baseline[a]**	**4**	**8**	**32**
Treatment-effectiveness[b]	30.5 (24.8)	–3.0 (33.3)	6.3 (37.0)	15.5 (29.8)
Emotional impact[b]	62.2 (24.5)	5.6 (16.7)	10.5 (17.9)	14.4 (17.9)
Daily activities[b]	75.1 (17.0)	–0.8 (15.8)	0.6 (13.7)	6.4 (17.8)
Impact on work[b]	60.5 (27.2)	11.0 (25.4)	21.3 (23.1)	26.2 (24.4)
Treatment-bother[b]	68.2 (20.7)	0.4 (25.5)	7.3 (21.1)	3.2 (20.0)
Symptom-bother[c]	55.6 (18.9)	–4.7 (16.9)	–6.5 (17.1)	–12.5 (13.2)

IDEEL, Impact of Dry Eye on Everyday Life; SD, standard deviation. [a]Absolute baseline value.
[b]Higher scores indicate improvement. [c]Lower scores indicate improvement.

Supplementary Table S3. Change From Baseline in EQ-5D-5L Questionnaire Subscores

	Study visit, week			
Subscore, mean (SD)	**Baseline[a]**	**4**	**8**	**32**
Anxiety/Depression	1.73 (0.9)	0.06 (0.6)	–0.18 (0.5)	–0.21 (0.8)
Mobility	1.81 (0.9)	–0.09 (0.7)	–0.06 (0.7)	–0.11 (0.7)
Pain/Discomfort	2.24 (0.9)	–0.03 (0.9)	0.03 (0.9)	–0.04 (0.9)
Self-care	1.19 (0.6)	0.06 (0.4)	0.09 (0.5)	–0.11 (0.4)
Usual activities	1.78 (0.9)	0.06 (0.9)	–0.24 (0.7)	–0.11 (0.8)

EQ-5D-5L, EuroQoL 5-dimension 5-level; SD, standard deviation. [a]Absolute baseline value.