Clinical trial results:
A 4 week, Phase III, multicenter, double-masked, vehicle-controlled study to evaluate safety and efficacy of Cenegermin (Oxervate®) 20 mcg/mL ophthalmic solution versus vehicle, in patients with severe Sjogren's dry eye disease under treatment with Cyclosporine A (PROTEGO-2 study)

Summary

EudraCT number	2021-003749-39
Trial protocol	IT
Global end of trial date	24 May 2023

Results information

Result version number	v1 (current)
This version publication date	08 May 2024
First version publication date	08 May 2024

Trial information

Trial identification

Sponsor protocol code	NGF0221

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05136170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici S.p.A.
Sponsor organisation address	Via Santa Lucia, 6, Milano, Italy, 20122
Public contact	Flavio Mantelli, Dompé farmaceutici S.p.A., +39 08623381, flavio.mantelli@dompe.com
Scientific contact	Flavio Mantelli, Dompé farmaceutici S.p.A., +39 08623381, flavio.mantelli@dompe.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2023
Global end of trial reached?	Yes
Global end of trial date	24 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective was to assess the efficacy and safety of cenegermin (rhNGF) ophthalmic solution at 20 mcg/mL concentration administered three times daily (TID) for four weeks in patients with severe Sjogren's dry eye disease (DED) who were under treatment with topical Cyclosporine A (CsA) or other drugs of the same class.

Protection of trial subjects:

The study was conducted in full compliance with applicable legislation, Food and Drug Administration (FDA), European Medicine Agency (EMA) and International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR Section 312.120.
Eligible patients took part in the study after providing the written informed consent approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB). Informed consent was obtained before starting any procedure pertaining to the study (i.e., all the procedures described in the protocol). A Patient Information Sheet and informed consent form (ICF), which met regulatory requirements and were appropriate for this study, were provided to the patient. Each patient read or was read (if he or she could not read or write), assent understanding of, and sign or thumb-printed an instrument of informed consent and after having had an opportunity to discuss them with the Principal Investigator (PI) before signing; each patient was made aware that he or she could withdraw from the study at any time.
Patients could voluntarily discontinue treatment with the IMP(s) for any reason at any time. Patients could be withdrawn from treatment with the IMP and assessments at any time, if deemed necessary by the Investigator. The investigator advised patients that prematurely discontinued on any therapies or treatments for their condition and referred them for further treatment, as appropriate.
Before the trial formally started, Dompé farmaceutici S.p.A. took out a study-specific insurance contract according to national laws for patients/Investigators/Institutions participating in the clinical trial.

Background therapy:

If strictly needed, the patient could take preservative free artificial tears (provided by the Sponsor).
One drop of Blink® Tears or equivalent was instilled in both eyes during the screening week, only if strictly needed by the patient. The patient documented in the patient's Diary the number of additional drops administered for each eye.
One drop of Blink® Tears or equivalent was instilled in both eyes during the four weeks of masked treatment, only if strictly needed by the patient. The patient documented in the patient's Diary the number of additional drops administered for each eye.
One drop of Blink® Tears or equivalent was instilled in both eye TID (morning, afternoon, and evening) during the initially eight weeks of follow-up. The patient, only if strictly needed, could administer additional drops and had to document in the patient's Diary the number of additional drops administered for each eye.

Evidence for comparator:

As part of the development plan, the present study was designed to evaluate the safety and efficacy of Oxervate® (cenegermin ophthalmic solution, rhNGF) vs vehicle in patients with severe Sjogren's DED under treatment with Cyclosporine A.
No particular safety risks are foreseen with respect to the safety profile of the marketed product Oxervate® (cenegermin 20 mcg/mL ophthalmic solution). The patients with severe Sjogren's DED participating in this study could potentially benefit from the application of cenegermin.

Actual start date of recruitment	17 March 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Italy: 43
Worldwide total number of subjects	85
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	62
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Three sites in Italy and 7 sites in US enrolled patients. A total of 97 patients were assessed for eligibility. There were 12 screening failures. The remaining patients (n=85) were randomized 1:1 as follows: 44 to cenegermin and 41 to vehicle. One patient in the vehicle group did not receive study medication and was excluded from the SAF and FAS.

Pre-assignment

Screening details:

Adults (≥ 18 years) with a diagnosis of severe Sjögren's DED, characterized by: corneal and/or conjunctival staining with fluorescein using NEI grading system ≥3, SANDE questionnaire >25 mm, Schirmer test I (without anaesthesia) ≥2 ≤5mm/5min. BCDVA score ≥ 0.1 decimal units (20/200 Snellen value) in each eye at enrolment. Under treatment with CsA.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a double-blind study. Blinding was ensured as described in the Study Protocol: vials containing cenegermin or vehicle were identical in appearance, and the contents of the vials were indistinguishable. All staff directly involved in the analysis of study results remained masked to treatment assignments while the study was in progress. The blind was not broken for any patient during the study before the database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cenegermin

Arm description:

Group 1: Cenegermin (rhNGF 20 mcg/mL)

Arm type	Experimental
Investigational medicinal product name	Cenegermin
Investigational medicinal product code	
Other name	Oxervate®, rhNGF
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop of cenegermin 20 mcg/mL was instilled in both eyes TID (every six hours, e.g., 7:00 am, 01:00 pm; 07:00 pm).

Arm title	Vehicle

Arm description:

Group 2: Placebo vehicle (Vehicle vials). Out of the 41 patients enrolled in the study and assigned to the vehicle treatment group, one patient did not receive any dose of study medication and was therefore excluded from the SAF and FAS populations. Thus, results are reported for the 40 patients in the vehicle group who received treatment.

Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop of vehicle ophthalmic solution was instilled in both eyes TID (every six hours, e.g., 7:00 am, 01:00 pm; 07:00 pm).

Number of subjects in period 1[1]	Cenegermin	Vehicle
Started	44	40
Completed	41	39
Not completed	3	1
Consent withdrawn by subject	2	1
Can no longer make office visits	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of the 85 patients enrolled in the study, one patient in the vehicle group was excluded from the SAF and FAS populations because this patient did not receive any dose of study medication. Therefore, both SAF and FAS populations consisted of 84 patients: 44 patients in the cenegermin group and 40 patients in the vehicle group.

Baseline characteristics

Reporting groups	
Reporting group title	Cenegermin
Reporting group description:	
Group 1: Cenegermin (rhNGF 20 mcg/mL)	
Reporting group title	Vehicle
Reporting group description:	
Group 2: Placebo vehicle (Vehicle vials). Out of the 41 patients enrolled in the study and assigned to the vehicle treatment group, one patient did not receive any dose of study medication and was therefore excluded from the SAF and FAS populations. Thus, results are reported for the 40 patients in the vehicle group who received treatment.	

Reporting group values	Cenegermin	Vehicle	Total
Number of subjects	44	40	84
Age categorical Units: Subjects			
Adults (18-64 years)	35	27	62
From 65-84 years	9	13	22
Age continuous Units: years			
arithmetic mean	55.0	58.1	
standard deviation	± 13.93	± 12.84	-
Gender categorical Units: Subjects			
Female	38	35	73
Male	6	5	11
Geographic region Units: Subjects			
Europe	23	19	42
US	21	21	42
Site Units: Subjects			
Site #01	9	7	16
Site #02	4	3	7
Site #04	10	9	19
Site #05	4	5	9
Site #06	1	0	1
Site #07	2	1	3
Site #08	2	4	6
Site #09	3	3	6
Site #10	6	6	12
Site #12	3	2	5
Race Units: Subjects			
Asian	0	4	4
Unknown	0	1	1
Black or African American	4	4	8
White	37	30	67
Other	2	1	3

Missing	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	41	38	79

End points

End points reporting groups

Reporting group title	Cenegermin
Reporting group description:	
Group 1: Cenegermin (rhNGF 20 mcg/mL)	
Reporting group title	Vehicle
Reporting group description:	
Group 2: Placebo vehicle (Vehicle vials). Out of the 41 patients enrolled in the study and assigned to the vehicle treatment group, one patient did not receive any dose of study medication and was therefore excluded from the SAF and FAS populations. Thus, results are reported for the 40 patients in the vehicle group who received treatment.	

Primary: Schirmer I test (without anaesthesia) >10mm/5min at Week 4

End point title	Schirmer I test (without anaesthesia) >10mm/5min at Week 4
End point description:	
Patients achieving Schirmer I test (without anaesthesia) value of >10mm/5min at Week 4	
End point type	Primary
End point timeframe:	
Week 4	

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Subjects	19	4		

Statistical analyses

Statistical analysis title	Logistic Regression Model
Statistical analysis description:	
Analysis is based on logistic regression model with multiple imputation (MI) under a missing not at random (MNAR) mechanism using retrieve dropouts with proportion of patients reaching a value of Schirmer I test > 10 mm/5 min at Week 4 as dependent variable, treatment, gender, age class and baseline Schirmer I test value as qualitative independent variables. Site is considered as random effects that vary randomly among patients.	
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.498

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.165
upper limit	33.356

Primary: Change from Baseline in the Global SANDE Score at Week 12

End point title	Change from Baseline in the Global SANDE Score at Week 12

End point description:

Change from Baseline in the Global SANDE score at Week 12, analysis of covariance (ANCOVA). Results described below refer to the adjusted means from the ANCOVA model.

End point type	Primary

End point timeframe:

Week 12

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-12.452 (-19.962 to -4.942)	-13.042 (-20.650 to -5.433)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis is based on ANCOVA model with multiple imputation (MI) under a missing not at random (MNAR) mechanism using retrieve dropouts with change from baseline in the global SANDE score at Week 12 as dependent variable, treatment, gender, age class and baseline global SANDE score as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89 [1]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.801
upper limit	8.981

Notes:

[1] - Adjusted means difference [95% CI] between the two groups (0.590 [-7.801; 8.981]) was not statistically significant (p-value = 0.890).

Secondary: Schirmer I test (without anaesthesia) >10mm/5min at Week 8

End point title	Schirmer I test (without anaesthesia) >10mm/5min at Week 8

End point description:

KEY SECONDARY ENDPOINT: Patients achieving Schirmer I test value of >10mm/5min at Week 8

End point type	Secondary

End point timeframe:

Week 8

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Subjects	11	2		

Statistical analyses

Statistical analysis title	Logistic Regression Model

Statistical analysis description:

Analysis is based on logistic regression model with multiple imputation (MI) under missing not at random (MNAR) using retrieve dropouts with proportion of patients reaching a value of Schirmer I test > 10 mm/5 min at Week 8 as dependent variable, treatment, gender, age class and baseline Schirmer I test value as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.648
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.307
upper limit	33.808

Secondary: Change from Baseline in Symptoms Questionnaire (SANDE) Score for Severity at Week 12

End point title	Change from Baseline in Symptoms Questionnaire (SANDE) Score for Severity at Week 12

End point description:

KEY SECONDARY ENDPOINT: Change from Baseline in SANDE scores for Severity at Week 12, analysis of covariance (ANCOVA). Results described below refer to the adjusted means from the ANCOVA model.

End point type	Secondary

End point timeframe:

Week 12

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from Baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-11.851 (-19.824 to -3.878)	-12.072 (-20.188 to -3.957)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis is based on ANCOVA model with multiple imputation (MI) under missing not at random (MNAR) using retrieve dropouts with change from baseline in the severity SANDE score at Week 12 as dependent variable, treatment, gender, age class and baseline severity SANDE score as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.962 [2]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	0.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.934
upper limit	9.377

Notes:

[2] - The adjusted mean change from baseline in the cenegermin group was not statistically significantly superior to that in the vehicle group (p-value = 0.962).

Secondary: Change from Baseline in Symptoms Questionnaire (SANDE) Score for Frequency at Week 12

End point title	Change from Baseline in Symptoms Questionnaire (SANDE) Score for Frequency at Week 12

End point description:

KEY SECONDARY ENDPOINT: Change from Baseline in SANDE scores for Frequency at Week 12 , analysis of covariance (ANCOVA). Results described below refer to the adjusted means from the ANCOVA model.

End point type	Secondary

End point timeframe:

Week 12.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-14.606 (-23.007 to -6.204)	-14.770 (-23.258 to -6.281)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis is based on ANCOVA model with multiple imputation (MI) under missing not at random (MNAR) using retrieve dropouts with change from baseline in the frequency SANDE score at Week 12 as dependent variable, treatment, gender, age class and baseline frequency SANDE score as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.973 [3]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.221
upper limit	9.549

Notes:

[3] - The adjusted means difference between the two groups was not statistically significant (p-value = 0.973).

Secondary: Change from Baseline in IDEEL modules (Quality Of Life, Dry Eye Treatment Satisfaction & Bother and Dry Eye Symptom-Bother modules) at Week 12 and at Week 4

End point title	Change from Baseline in IDEEL modules (Quality Of Life, Dry Eye Treatment Satisfaction & Bother and Dry Eye Symptom-Bother modules) at Week 12 and at Week 4

End point description:

KEY SECONDARY ENDPOINT: Change from Baseline at Week 12 and at Week 4 in IDEEL modules, including Quality Of Life (QoL), Dry Eye Treatment Satisfaction & Bother (TS) and Dry Eye Symptom-Bother modules.

End point type	Secondary

End point timeframe:

Week 12 and Week 4.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Changes from baseline in IDEEL modules				
least squares mean (confidence interval 95%)				
QoL (Daily activities) - Week 4	13.690 (8.034 to 19.346)	11.312 (5.393 to 17.231)		
QoL (Daily activities) - Week 12	13.769 (7.711 to 19.827)	6.659 (0.549 to 12.769)		
QoL (Feelings) - Week 4	8.811 (2.356 to 15.266)	12.977 (6.263 to 19.692)		
QoL (Feelings) - Week 12	11.413 (5.058 to 17.767)	10.355 (3.923 to 16.787)		
QoL (Work) - Week 4	10.689 (2.183 to 19.195)	14.596 (5.224 to 23.967)		
QoL (Work) - Week 12	13.225 (5.547 to 20.903)	13.509 (5.084 to 21.934)		
TS (Treatment - in general) - Week 4	8.708 (2.786 to 14.630)	8.757 (2.493 to 15.022)		
TS (Treatment - in general) - Week 12	7.281 (1.570 to 12.992)	5.305 (-0.513 to 11.124)		
TS (Treatment - Eye drops) - Week 4	11.368 (3.535 to 19.202)	8.598 (0.287 to 16.908)		
TS (Treatment - Eye drops) - Week 12	11.447 (3.576 to 19.318)	6.193 (-1.781 to 14.167)		
Symptom-Bother - Week 4	-8.030 (-13.302 to -2.758)	-13.262 (-18.758 to -7.766)		
Symptom-Bother - Week 12	-10.814 (-16.220 to -5.407)	-10.657 (-16.102 to -5.212)		

Statistical analyses

Statistical analysis title	QoL (Daily activities) - Week 4

Statistical analysis description:

Analysis is based on MMRM with multiple Imputation (MI) under missing not at random using (MNAR) retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52 [4]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	2.378
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.869
upper limit	9.625

Notes:

[4] - Not statistically significant result.

Statistical analysis title	QoL (Daily activities) - Week 12

Statistical analysis description:

Analysis is based on MMRM with multiple Imputation (MI) under missing not at random using (MNAR) retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073 [5]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	7.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.653
upper limit	14.873

Notes:

[5] - Not statistically significant result.

Statistical analysis title	QoL (Feelings) - Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.317 [6]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-4.166

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.322
upper limit	3.989

Notes:

[6] - Not statistically significant result.

Statistical analysis title	QoL (Feelings) - Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.792 [7]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.786
upper limit	8.901

Notes:

[7] - Not statistically significant result.

Statistical analysis title	QoL (Work) - Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488 [8]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-3.907
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.948
upper limit	7.135

Notes:

[8] - Not statistically significant result.

Statistical analysis title	QoL (Work) - Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Quality of life module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.954 [9]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.998
upper limit	9.431

Notes:

[9] - Not statistically significant result.

Statistical analysis title	TS (Treatment - in general) - Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Treatment satisfaction & Bother module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 [10]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.658
upper limit	7.559

Notes:

[10] - Not statistically significant result.

Statistical analysis title	TS (Treatment - in general) - Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Treatment satisfaction & Bother module at each

timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582 [11]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.976
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.065
upper limit	9.017

Notes:

[11] - Not statistically significant result.

Statistical analysis title	TS (Treatment - Eye drops) - Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Treatment satisfaction & Bother module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586 [12]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	2.771
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.213
upper limit	12.754

Notes:

[12] - Not statistically significant result.

Statistical analysis title	TS (Treatment - Eye drops) - Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Treatment satisfaction & Bother module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29 [13]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	5.254
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.488
upper limit	14.996

Notes:

[13] - Not statistically significant result.

Statistical analysis title	Symptom-Bother - Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Symptom bother module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125 [14]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	5.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.457
upper limit	11.922

Notes:

[14] - Not statistically significant result.

Statistical analysis title	Symptom-Bother - Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in IDEEL Dry eye Symptom bother module at each timepoint adjusting by gender, age class, IDEEL scale baseline value, treatment, visit, and treatment by visit interaction. Subject was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.964 [15]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.156

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.912
upper limit	6.6

Notes:

[15] - Not statistically significant result.

Secondary: Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 4, Week 8 and Week 12

End point title	Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 4, Week 8 and Week 12

End point description:

KEY SECONDARY ENDPOINT: Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein NEI scale up to Week 12, MMRM.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from baseline				
least squares mean (confidence interval 95%)				
Week 4	-3.331 (-4.725 to -1.938)	-2.354 (-3.889 to -0.819)		
Week 8	-3.102 (-4.439 to -1.765)	-2.445 (-3.897 to -0.993)		
Week 12	-3.595 (-4.987 to -2.203)	-3.571 (-5.048 to -2.094)		

Statistical analyses

Statistical analysis title	Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in Cornea and conjunctiva vital staining with fluorescein NEI scale at each timepoint adjusting by gender, age class, NEI scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [16]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.977
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.749
upper limit	0.795

Notes:

[16] - Not statistically significant result.

Statistical analysis title	Week 8

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in Cornea and conjunctiva vital staining with fluorescein NEI scale at each timepoint adjusting by gender, age class, NEI scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [17]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.324
upper limit	1.01

Notes:

[17] - Not statistically significant result.

Statistical analysis title	Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in Cornea and conjunctiva vital staining with fluorescein NEI scale at each timepoint adjusting by gender, age class, NEI scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978 [18]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.024

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.743
upper limit	1.694

Notes:

[18] - Not statistically significant result.

Secondary: Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 4, Week 8 and Week 12

End point title	Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 4, Week 8 and Week 12

End point description:

KEY SECONDARY ENDPOINT: Change from Baseline in TFBUT up to Week 12, MMRM.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from baseline in TFBUT				
least squares mean (confidence interval 95%)				
Week 4	1.020 (0.253 to 1.787)	0.225 (-0.586 to 1.036)		
Week 8	0.899 (0.074 to 1.725)	0.951 (0.088 to 1.813)		
Week 12	0.917 (0.123 to 1.711)	0.782 (-0.040 to 1.603)		

Statistical analyses

Statistical analysis title	Week 4

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in TFBUT at each timepoint adjusting by gender, age class, TFBUT scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102 [19]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	0.795

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.157
upper limit	1.748

Notes:

[19] - Not statistically significant result.

Statistical analysis title	Week 8

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in TFBUT at each timepoint adjusting by gender, age class, TFBUT scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.923 [20]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.094
upper limit	0.991

Notes:

[20] - Not statistically significant result.

Statistical analysis title	Week 12

Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation under missing not at random using retrieve dropouts with change from baseline in TFBUT at each timepoint adjusting by gender, age class, TFBUT scale baseline value, treatment, visit, and treatment by visit interaction. Patient was considered as a random effect and the covariance matrix used was unstructured

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.787 [21]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.849
upper limit	1.12

Notes:

[21] - Not statistically significant result.

Secondary: Change from Baseline in Schirmer I Test (without anaesthesia) at Week 4, Week 8, Week 12, and Week 16

End point title	Change from Baseline in Schirmer I Test (without anaesthesia) at Week 4, Week 8, Week 12, and Week 16

End point description:

Change from Baseline in Schirmer I Test at each Timepoint.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12 and Week 16.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[22]	40[23]		
Units: Change from baseline in Schirmer I Test				
arithmetic mean (standard deviation)				
Week 4	5.4 (± 5.2)	1.7 (± 3.2)		
Week 8	4.9 (± 4.5)	1.5 (± 3.0)		
Week 12	4.1 (± 4.7)	3.1 (± 6.3)		
Week 16	3.4 (± 4.0)	2.4 (± 4.9)		

Notes:

[22] - Week 4, n=43; Week 8, n=40; Week 12, n=40; Week 16, n=41.

[23] - Week 4, n=39; Week 8, n=38; Week 12, n=39; Week 16, n=38.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.001 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.

[25] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.001 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - 84 subjects are included in the FAS, however only 78 subjects are analyzed in this table due to the presence of missing values.

[27] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of

the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.014 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[29] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.095 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[31] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Secondary: Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 4, Week 8, Week 12 and Week 16

End point title	Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 4, Week 8, Week 12 and Week 16

End point description:

Change from baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (NEI scale) at each Timepoint

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12 and Week 16

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[32]	40[33]		
Units: Change from baseline in NEI scale				
arithmetic mean (standard deviation)				
Week 4	-3.6 (± 4.6)	-2.4 (± 4.7)		
Week 8	-3.1 (± 3.8)	-2.9 (± 3.9)		
Week 12	-3.4 (± 4.6)	-3.0 (± 3.8)		

Week 16	-2.0 (± 6.9)	-2.3 (± 4.2)		

Notes:

[32] - Week 4, n=42; Week 8, n=39; Week 12, n=39; Week 16, n=40.

[33] - Week 4, n=37; Week 8, n=36; Week 12, n=37; Week 16, n=36.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.02 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.

[35] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.328 [37]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - 84 subjects are included in the FAS, however only 75 subjects are analyzed in this table due to the presence of missing values.

[37] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.287 [39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - 84 subjects are included in the FAS, however only 76 subjects are analyzed in this table due to the presence of missing values.

[39] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.777 [41]
Method	Wilcoxon (Mann-Whitney)

Notes:

[40] - 84 subjects are included in the FAS, however only 76 subjects are analyzed in this table due to the presence of missing values.
[41] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Secondary: Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 4, Week 8, Week 12 and Week 16

End point title	Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 4, Week 8, Week 12 and Week 16

End point description:

Change from baseline in TFBUT at each Timepoint.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12 and Week 16.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[42]	40[43]		
Units: Change from baseline in TFBUT				
arithmetic mean (standard deviation)				
Week 4	1.1 (± 2.4)	0.2 (± 2.2)		
Week 8	0.9 (± 2.5)	0.9 (± 2.3)		
Week 12	1.0 (± 2.6)	0.7 (± 1.8)		
Week 16	1.3 (± 2.8)	1.1 (± 2.5)		

Notes:

[42] - Week 4, n=43; Week 8, n=40; Week 12, n=40; Week 16, n=41.

[43] - Week 4, n=39; Week 8, n=38; Week 12, n=39; Week 16, n=38.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.126 [45]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[45] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and and Vehicle in all patients.

Statistical analysis title	Week 8
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.968 [47]
Method	t-test, 2-sided

Notes:

[46] - 84 subjects are included in the FAS, however only 78 subjects are analyzed in this table due to the presence of missing values.
[47] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and and Vehicle in all patients.

Statistical analysis title	Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.613 [49]
Method	t-test, 2-sided

Notes:

[48] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[49] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and and Vehicle in all patients.

Statistical analysis title	Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.805 [51]
Method	t-test, 2-sided

Notes:

[50] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[51] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and and Vehicle in all patients.

Secondary: Change from Baseline in Symptoms Questionnaire (SANDE) Global Scores, and for Severity and Frequency at Week 8, Week 12, and Week 16

End point title	Change from Baseline in Symptoms Questionnaire (SANDE) Global Scores, and for Severity and Frequency at Week 8, Week 12, and Week 16

End point description:

Change from baseline in SANDE Global scores, SANDE Severity scores and SANDE Frequency scores at each Timepoint.

End point type	Secondary

End point timeframe:

Week 8, Week 12, and Week 16

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[52]	40[53]		
Units: Change from baseline in SANDE scores				
arithmetic mean (standard deviation)				
Global Score - Week 8	-12.9 (± 19.0)	-10.3 (± 19.2)		
Global Score - Week 12	-9.5 (± 17.0)	-11.3 (± 22.5)		
Global Score - Week 16	-9.0 (± 22.3)	-11.1 (± 19.0)		
Severity - Week 8	-10.7 (± 19.6)	-9.9 (± 20.9)		
Severity - Week 12	-8.6 (± 19.6)	-10.2 (± 25.1)		
Severity - Week 16	-7.9 (± 22.9)	-10.2 (± 20.2)		
Frequency - Week 8	-16.4 (± 23.2)	-10.9 (± 21.2)		
Frequency - Week 12	-10.3 (± 23.6)	-12.3 (± 23.5)		
Frequency - Week 16	-10.5 (± 24.2)	-12.2 (± 18.6)		

Notes:

[52] - Week 8, n=40; Week 12, n=40; Week 16, n=41.

[53] - Week 8, n=38; Week 12, n=39; Week 16, n=38.

Statistical analyses

Statistical analysis title	Global Score - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.543 [55]
Method	t-test, 2-sided

Notes:

[54] - 84 subjects are included in the FAS, however only 78 subjects are analyzed in this table due to the presence of missing values.

[55] - Not statistically significant result. p-value corresponds to two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Global Score - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.677 [57]
Method	t-test, 2-sided

Notes:

[56] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.

[57] - Not statistically significant result. p-value corresponds to two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Global Score - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.914 [59]
Method	Wilcoxon (Mann-Whitney)

Notes:

[58] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[59] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Severity - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.874 [61]
Method	t-test, 2-sided

Notes:

[60] - 84 subjects are included in the FAS, however only 78 subjects are analyzed in this table due to the presence of missing values.
[61] - Not statistically significant result. p-value corresponds to two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Severity - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.945 [63]
Method	Wilcoxon (Mann-Whitney)

Notes:

[62] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[63] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Severity - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.727 [65]
Method	Wilcoxon (Mann-Whitney)

Notes:

[64] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[65] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Frequency - Week 8
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.342 [67]
Method	Wilcoxon (Mann-Whitney)

Notes:

[66] - 84 subjects are included in the FAS, however only 78 subjects are analyzed in this table due to the presence of missing values.
[67] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Frequency - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.821 [69]
Method	Wilcoxon (Mann-Whitney)

Notes:

[68] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[69] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Frequency - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.926 [71]
Method	Wilcoxon (Mann-Whitney)

Notes:

[70] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[71] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Secondary: Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Scores) and/or NEI Score ≥ 50% at Week 4

End point title	Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Scores) and/or NEI Score ≥ 50% at Week 4

End point description:

Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score ≥50% at Week 4.

End point type	Secondary

End point timeframe:

Week 4

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[72]	40[73]		
Units: Subjects				
Worsening in symptom scores (SANDE global score)	14	5		
NEI score >= 50%	1	1		
Worsening in symptom scores and/or NEI score >= 50	15	5		

Notes:

[72] - Wors. Symptom scores, n=43; NEI score ≥50%, n=42; Wors. symptom scores and/or NEI score ≥50%, n=42.
[73] - Wors. Symptom scores, n=39; NEI score ≥50%, n=37; Wors. symptom scores and/or NEI score ≥50%, n=37.

Statistical analyses

Statistical analysis title	Worsening in symptom scores (SANDE global score)
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.0344 [75]
Method	Chi-squared

Notes:

[74] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[75] - p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	NEI score >= 50%
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 1 [77]
Method	Fisher exact

Notes:

[76] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[77] - Not statistically significant result. p-value corresponds to a Fisher`s exact test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Worsening in symptom scores and/or NEI score >= 50
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.0235 [79]
Method	Chi-squared

Notes:

[78] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[79] - p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients.

Secondary: IDEEL Questionnaire at Week 4, Week, 8, Week 12, and Week 16

End point title	IDEEL Questionnaire at Week 4, Week, 8, Week 12, and Week 16

End point description:

Change from baseline in IDEEL Quality of Life (QoL) module, Treatment Satisfaction (TS) module, and Symptom-Bother module at each Timepoint.

End point type	Secondary

End point timeframe:

Week 4, Week, 8, Week 12, and Week 16.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Change from baseline in IDEEL score				
arithmetic mean (standard deviation)				
QoL (Impact on Daily Activities) - Week 4	10.9 (± 20.7)	10.3 (± 16.4)		
QoL (Impact on Daily Activities) - Week 8	9.2 (± 20.6)	7.2 (± 17.0)		
QoL (Impact on Daily Activities) - Week 12	11.9 (± 20.8)	5.6 (± 19.3)		
QoL (Impact on Daily Activities) - Week 16	10.8 (± 19.6)	8.1 (± 16.2)		
QoL (Emotional Impact due to Dry Eye) - Week 4	4.3 (± 21.6)	10.1 (± 17.5)		
QoL (Emotional Impact due to Dry Eye) - Week 8	6.1 (± 20.0)	8.5 (± 16.0)		
QoL (Emotional Impact due to Dry Eye) - Week 12	7.4 (± 21.8)	7.4 (± 16.6)		
QoL (Emotional Impact due to Dry Eye) - Week 16	6.7 (± 25.0)	7.6 (± 16.1)		
QoL (Impact on Work due to Dry Eye) - Week 4	9.8 (± 24.7)	13.4 (± 16.1)		
QoL (Impact on Work due to Dry Eye) - Week 8	9.5 (± 21.7)	8.1 (± 14.3)		
QoL (Impact on Work due to Dry Eye) - Week 12	10.4 (± 19.9)	11.8 (± 20.0)		
QoL (Impact on Work due to Dry Eye) - Week 16	13.6 (± 21.3)	8.9 (± 15.1)		
TS (Satisfaction with Effectiveness) - Week 4	11.3 (± 30.4)	10.1 (± 25.1)		
TS (Satisfaction with Effectiveness) - Week 8	12.0 (± 25.5)	5.2 (± 25.2)		
TS (Satisfaction with Effectiveness) - Week 12	13.1 (± 26.8)	7.4 (± 25.7)		
TS (Satisfaction with Effectiveness) - Week 16	13.1 (± 29.0)	7.9 (± 26.1)		
TS (Treatment Bother/Inconvenience) - Week 4	5.5 (± 21.7)	6.2 (± 12.7)		
TS (Treatment Bother/Inconvenience) - Week 8	3.3 (± 18.9)	5.0 (± 14.8)		
TS (Treatment Bother/Inconvenience) - Week 12	4.5 (± 19.8)	4.2 (± 12.4)		
TS (Treatment Bother/Inconvenience) - Week 16	5.4 (± 18.5)	3.3 (± 11.3)		

Symptom-Bother - Week 4	-5.8 (± 18.7)	-11.9 (± 12.5)		
Symptom-Bother - Week 8	-7.2 (± 16.4)	-7.9 (± 12.9)		
Symptom-Bother - Week 12	-8.6 (± 15.5)	-9.5 (± 17.7)		
Symptom-Bother - Week 16	-8.0 (± 17.0)	-9.2 (± 13.9)		

Statistical analyses

Statistical analysis title	QoL (Impact on Daily Activities) - Week 4
Comparison groups	Vehicle v Cenegermin
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.888 [81]
Method	t-test, 2-sided

Notes:

[80] - 84 subjects are included in the FAS, however only 81 subjects (Cenegermin, n=43; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[81] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Daily Activities) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 0.651 [83]
Method	t-test, 2-sided

Notes:

[82] - 84 subjects are included in the FAS, however only 77 subjects (Cenegermin, n=40; Vehicle, n=37) are analyzed in this table due to the presence of missing values.
[83] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Daily Activities) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.267 [85]
Method	Wilcoxon (Mann-Whitney)

Notes:

[84] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=40; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[85] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Daily Activities) - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 0.459 [87]
Method	Wilcoxon (Mann-Whitney)

Notes:

[86] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=41; Vehicle, n=37) are analyzed in this table due to the presence of missing values.
[87] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Emotional Impact due to Dry Eye) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	= 0.192 [89]
Method	t-test, 2-sided

Notes:

[88] - 84 subjects are included in the FAS, however only 82 subjects (Cenegermin, n=43; Vehicle, n=39) are analyzed in this table due to the presence of missing values.
[89] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Emotional Impact due to Dry Eye) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[90]
P-value	= 0.568 [91]
Method	t-test, 2-sided

Notes:

[90] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=40; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[91] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Emotional Impact due to Dry Eye) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[92]
P-value	= 0.871 [93]
Method	Wilcoxon (Mann-Whitney)

Notes:

[92] - 84 subjects are included in the FAS, however only 79 subjects (Cenegermin, n=40; Vehicle, n=39) are analyzed in this table due to the presence of missing values.
[93] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Emotional Impact due to Dry Eye) - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[94]
P-value	= 0.85 [95]
Method	t-test, 2-sided

Notes:

[94] - 84 subjects are included in the FAS, however only 79 subjects (Cenegermin, n=41; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[95] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Work due to Dry Eye) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	= 0.364 [97]
Method	Wilcoxon (Mann-Whitney)

Notes:

[96] - 84 subjects are included in the FAS, however only 49 subjects (Cenegermin, n=27; Vehicle, n=22) are analyzed in this table due to the presence of missing values.
[97] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Work due to Dry Eye) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[98]
P-value	= 0.646 [99]
Method	Wilcoxon (Mann-Whitney)

Notes:

[98] - 84 subjects are included in the FAS, however only 49 subjects (Cenegermin, n=28; Vehicle, n=21) are analyzed in this table due to the presence of missing values.
[99] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Work due to Dry Eye) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[100]
P-value	= 0.739 [101]
Method	Wilcoxon (Mann-Whitney)

Notes:

[100] - 84 subjects are included in the FAS, however only 49 subjects (Cenegermin, n=27; Vehicle, n=22) are analyzed in this table due to the presence of missing values.
[101] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	QoL (Impact on Work due to Dry Eye) - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[102]
P-value	= 0.664 [103]
Method	Wilcoxon (Mann-Whitney)

Notes:

[102] - 84 subjects are included in the FAS, however only 50 subjects (Cenegermin, n=28; Vehicle, n=22) are analyzed in this table due to the presence of missing values.
[103] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Satisfaction with Effectiveness) - Week 4
Comparison groups	Vehicle v Cenegermin
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[104]
P-value	= 0.846 [105]
Method	t-test, 2-sided

Notes:

[104] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=42; Vehicle, n=36) are analyzed in this table due to the presence of missing values.
[105] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Satisfaction with Effectiveness) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[106]
P-value	= 0.248 [107]
Method	t-test, 2-sided

Notes:

[106] - 84 subjects are included in the FAS, however only 76 subjects (Cenegermin, n=39; Vehicle, n=37) are analyzed in this table due to the presence of missing values.
[107] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Satisfaction with Effectiveness) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[108]
P-value	= 0.341 [109]
Method	t-test, 2-sided

Notes:

[108] - 84 subjects are included in the FAS, however only 77 subjects (Cenegermin, n=39; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[109] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Satisfaction with Effectiveness) - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[110]
P-value	= 0.413 [111]
Method	t-test, 2-sided

Notes:

[110] - 84 subjects are included in the FAS, however only 77 subjects (Cenegermin, n=40; Vehicle, n=37) are analyzed in this table due to the presence of missing values.
[111] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Treatment Bother/Inconvenience) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[112]
P-value	= 0.927 [113]
Method	Wilcoxon (Mann-Whitney)

Notes:

[112] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=43; Vehicle, n=35) are analyzed in this table due to the presence of missing values.
[113] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Treatment Bother/Inconvenience) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[114]
P-value	= 0.914 [115]
Method	Wilcoxon (Mann-Whitney)

Notes:

[114] - 84 subjects are included in the FAS, however only 75 subjects (Cenegermin, n=39; Vehicle, n=36) are analyzed in this table due to the presence of missing values.
[115] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Treatment Bother/Inconvenience) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[116]
P-value	= 0.564 [117]
Method	Wilcoxon (Mann-Whitney)

Notes:

[116] - 84 subjects are included in the FAS, however only 76 subjects (Cenegermin, n=39; Vehicle, n=37) are analyzed in this table due to the presence of missing values.
[117] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	TS (Treatment Bother/Inconvenience) - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[118]
P-value	= 0.489 [119]
Method	Wilcoxon (Mann-Whitney)

Notes:

[118] - 84 subjects are included in the FAS, however only 75 subjects (Cenegermin, n=39; Vehicle, n=36) are analyzed in this table due to the presence of missing values.
[119] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Symptom-Bother - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[120]
P-value	= 0.082 [121]
Method	t-test, 2-sided

Notes:

[120] - 84 subjects are included in the FAS, however only 82 subjects (Cenegermin, n=43; Vehicle, n=39) are analyzed in this table due to the presence of missing values.
[121] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Symptom-Bother - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[122]
P-value	= 0.848 [123]
Method	t-test, 2-sided

Notes:

[122] - 84 subjects are included in the FAS, however only 78 subjects (Cenegermin, n=40; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[123] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Symptom-Bother - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[124]
P-value	= 0.805 [125]
Method	t-test, 2-sided

Notes:

[124] - 84 subjects are included in the FAS, however only 79 subjects (Cenegermin, n=40; Vehicle, n=39) are analyzed in this table due to the presence of missing values.
[125] - Not statistically significant result. p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Symptom-Bother - Week 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[126]
P-value	= 0.833 [127]
Method	Wilcoxon (Mann-Whitney)

Notes:

[126] - 84 subjects are included in the FAS, however only 79 subjects (Cenegermin, n=41; Vehicle, n=38) are analyzed in this table due to the presence of missing values.
[127] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Proportion and Frequency of Preservative Free Artificial Tears Use (number of drops/day)

End point title	Proportion and Frequency of Preservative Free Artificial Tears Use (number of drops/day)

End point description:

Use of Preservative Free Artificial Tears by Study Period is calculated as: total number of drops of the preservative free artificial tears during the X period/ total number of days of the X period * 100.

End point type	Other pre-specified

End point timeframe:

Treatment Period, Follow-up Period and Overall

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[128]	40[129]		
Units: Preservative Free Artificial Tears				
arithmetic mean (standard deviation)				
Treatment Period	261.2 (± 220.2)	215.7 (± 184.7)		
Follow-up Period	330.0 (± 178.1)	317.6 (± 168.3)		
Overall	294.7 (± 202.5)	268.1 (± 182.6)		

Notes:

[128] - Treatment period, n=40; Follow-up period, n=38; Overall, n=41.

[129] - Treatment period, n=35; Follow-up period, n=37; Overall, n=38.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Schirmer I Test (without anaesthesia) at Week 2

End point title	Change from Baseline in Schirmer I Test (without anaesthesia) at Week 2

End point description:

Change from Baseline in Schirmer I Test (without anaesthesia) at Week 2

End point type	Other pre-specified

End point timeframe:

Week 2

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[130]	40[131]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	4.4 (± 5.0)	1.0 (± 2.4)		

Notes:

[130] - N=43

[131] - N=39

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[132]
P-value	< 0.001 [133]
Method	Wilcoxon (Mann-Whitney)

Notes:

[132] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.

[133] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 2

End point title	Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 2

End point description:

Change from Baseline in Cornea and Conjunctiva Vital Staining with Fluorescein (National Eye Institute [NEI] scales) at Week 2.

End point type	Other pre-specified

End point timeframe:

Week 2.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[134]	40[135]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	-2.6 (± 4.8)	-2.0 (± 5.2)		

Notes:

[134] - N=42.

[135] - N=37.

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[136]
P-value	= 0.046 [137]
Method	Wilcoxon (Mann-Whitney)

Notes:

[136] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.

[137] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 2

End point title	Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 2

End point description:

Change from Baseline in Tear Film Break-Up Time (TFBUT) at Week 2.

End point type	Other pre-specified

End point timeframe:

Week 2.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[138]	40[139]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	0.7 (± 2.1)	0.2 (± 2.0)		

Notes:

[138] - N=43.

[139] - N=39.

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[140]
P-value	= 0.34 [141]
Method	Wilcoxon (Mann-Whitney)

Notes:

[140] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.

[141] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Change from Baseline in Symptoms Questionnaire (SANDE) Global Scores, and for Severity and Frequency at Week 2, and Week 4

End point title	Change from Baseline in Symptoms Questionnaire (SANDE) Global Scores, and for Severity and Frequency at Week 2, and Week 4

End point description: Change from Baseline in Symptoms Questionnaire (SANDE) Global Scores, and for Severity and Frequency at Week 2, and Week 4.	
End point type	Other pre-specified
End point timeframe: Week 2 and Week 4.	

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[142]	40[143]		
Units: Change from baseline				
arithmetic mean (standard deviation)				
Global Score - Change from baseline to Week 2	-2.1 (± 18.0)	-12.3 (± 13.7)		
Global Score - Change from baseline to Week 4	-11.5 (± 17.4)	-15.0 (± 18.0)		
Severity - Change from baseline to Week 2	-0.5 (± 20.1)	-12.3 (± 14.9)		
Severity - Change from baseline to Week 4	-9.2 (± 19.7)	-13.6 (± 17.2)		
Frequency - Change from baseline to Week 2	-3.8 (± 18.9)	-12.0 (± 14.7)		
Frequency - Change from baseline to Week 4	-14.5 (± 18.8)	-16.9 (± 22.2)		

Notes:

[142] - Week 2, n=43; Week 4, n=43.

[143] - Week 2, n=39; Week 4, n=39.

Statistical analyses

Statistical analysis title	Global Score - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[144]
P-value	= 0.017 [145]
Method	Wilcoxon (Mann-Whitney)

Notes:

[144] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.

[145] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Global Score - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[146]
P-value	= 0.339 [147]
Method	Wilcoxon (Mann-Whitney)

Notes:

[146] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[147] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Severity - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[148]
P-value	= 0.004 [149]
Method	t-test, 2-sided

Notes:

[148] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[149] - p-value corresponds to a two sample (independent group) t-test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Severity - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[150]
P-value	= 0.292 [151]
Method	Wilcoxon (Mann-Whitney)

Notes:

[150] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[151] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Frequency - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[152]
P-value	= 0.09 [153]
Method	Wilcoxon (Mann-Whitney)

Notes:

[152] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[153] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Frequency - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[154]
P-value	= 0.54 [155]
Method	Wilcoxon (Mann-Whitney)

Notes:

[154] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.

[155] - Not statistically significant result. p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score ≥ 50% assessed at Week 2	
End point title	Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score ≥ 50% assessed at Week 2
End point description:	
Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score ≥ 50% assessed at Week 2	
End point type	Other pre-specified
End point timeframe:	
Week 2.	

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[156]	40[157]		
Units: Subjects				
Worsening in symptom scores (SANDE global score)	17	5		
NEI score >= 50%	1	0		
Worsening in symptom scores and/or NEI score >= 50	18	5		

Notes:

[156] - Wors. Symptom scores, n=43; NEI score ≥50%, n=42; Wors. symptom scores and/or NEI score ≥50%, n=42.
[157] - Wors. Symptom scores, n=39; NEI score ≥50%, n=37; Wors. symptom scores and/or NEI score ≥50%, n=38.

Statistical analyses

Statistical analysis title	Worsening in symptom scores (SANDE global score)
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[158]
P-value	= 0.0064 [159]
Method	Chi-squared

Notes:

[158] - 84 subjects are included in the FAS, however only 82 subjects are analyzed in this table due to the presence of missing values.
[159] - p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	NEI score >= 50%
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[160]
P-value	= 1 [161]
Method	Fisher exact

Notes:

[160] - 84 subjects are included in the FAS, however only 79 subjects are analyzed in this table due to the presence of missing values.
[161] - Not statistically significant result. p-value corresponds to a Fisher`s exact test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	Worsening in symptom scores and/or NEI score >= 50
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[162]
P-value	= 0.0034 [163]
Method	Chi-squared

Notes:

[162] - 84 subjects are included in the FAS, however only 80 subjects are analyzed in this table due to the presence of missing values.
[163] - p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients.

Other pre-specified: Change from Baseline in Schirmer Test II (with topical Anaesthesia) at Week 4

End point title	Change from Baseline in Schirmer Test II (with topical Anaesthesia) at Week 4

End point description:

Change from Baseline in Schirmer Test II (with topical Anaesthesia) at Week 4.

End point type	Other pre-specified

End point timeframe:

Week 4.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[164]	40[165]		
Units: Change from baseline in Schirmer II test				
arithmetic mean (standard deviation)	4.3 (± 4.2)	1.4 (± 3.7)		

Notes:

[164] - N=42.

[165] - N=38.

Statistical analyses

Statistical analysis title	Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[166]
P-value	< 0.001 [167]
Method	Wilcoxon (Mann-Whitney)

Notes:

[166] - 84 subjects are included in the FAS, however only 80 subjects are analyzed in this table due to the presence of missing values.
[167] - p-value corresponds to a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test of the comparisons between Cenegermin and Vehicle in all participants.

Other pre-specified: Change from Baseline in Best corrected distance visual acuity (BCDVA)

End point title	Change from Baseline in Best corrected distance visual acuity (BCDVA)

End point description:

Change from baseline (CFB) in BCDVA at each timepoint.

End point type	Other pre-specified

End point timeframe:

Week 2, Week 4, Week 8, Week 12 and Week 16.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Subjects				
CFB to Week 2 - No change	32	29		
CFB to Week 2 - 20/63 to 20/40	0	1		
CFB to Week 2 - 20/50 to 20/40	0	1		
CFB to Week 2 - 20/40 to 20/25	1	1		
CFB to Week 2 - 20/32 to 20/20	1	0		
CFB to Week 2 - 20/32 to 20/25	1	1		
CFB to Week 2 - 20/25 to 20/20	3	2		
CFB to Week 2 - 20/20 to 20/16	2	0		
CFB to Week 2 - 20/20 to 20/25	1	2		
CFB to Week 2 - 20/16 to 20/12.5	0	1		
CFB to Week 2 - 20/16 to 20/20	1	0		
CFB to Week 2 - 20/16 to 20/25	1	0		
CFB to Week 2 - 20/16 to 20/32	0	1		
CFB to Week 4 - No change	31	33		
CFB to Week 4 - 20/63 to 20/40	0	1		
CFB to Week 4 - 20/40 to 20/25	1	1		
CFB to Week 4 - 20/40 to 20/32	1	0		
CFB to Week 4 - 20/32 to 20/20	0	1		
CFB to Week 4 - 20/32 to 20/25	1	0		
CFB to Week 4 - 20/25 to 20/20	3	2		
CFB to Week 4 - 20/20 to 20/25	3	0		
CFB to Week 4 - 20/20 to 20/32	1	0		
CFB to Week 4 - 20/16 to 20/20	2	0		
CFB to Week 4 - 20/16 to 20/32	0	1		
CFB to Week 8 - No change	26	29		

CFB to Week 8 - 20/63 to 20/40	0	1		
CFB to Week 8 - 20/50 to 20/40	0	1		
CFB to Week 8 - 20/40 to 20/20	0	1		
CFB to Week 8 - 20/40 to 20/25	1	0		
CFB to Week 8 - 20/40 to 20/32	1	0		
CFB to Week 8 - 20/40 to 20/50	1	0		
CFB to Week 8 - 20/32 to 20/20	1	0		
CFB to Week 8 - 20/32 to 20/25	1	1		
CFB to Week 8 - 20/25 to 20/20	2	1		
CFB to Week 8 - 20/25 to 20/32	1	0		
CFB to Week 8 - 20/20 to 20/16	2	1		
CFB to Week 8 - 20/20 to 20/25	2	2		
CFB to Week 8 - 20/16 to 20/20	2	0		
CFB to Week 8 - 20/16 to 20/32	0	1		
CFB to Week 12 - No change	29	30		
CFB to Week 12 - 20/63 to 20/80	0	1		
CFB to Week 12 - 20/50 to 20/63	0	1		
CFB to Week 12 - 20/40 to 20/20	0	1		
CFB to Week 12 - 20/40 to 20/32	1	0		
CFB to Week 12 - 20/32 to 20/20	1	0		
CFB to Week 12 - 20/32 to 20/25	1	1		
CFB to Week 12 - 20/25 to 20/20	3	1		
CFB to Week 12 - 20/25 to 20/32	1	0		
CFB to Week 12 - 20/20 to 20/16	0	1		
CFB to Week 12 - 20/20 to 20/25	1	2		
CFB to Week 12 - 20/20 to 20/32	1	0		
CFB to Week 12 - 20/16 to 20/20	1	0		
CFB to Week 12 - 20/16 to 20/50	0	1		
CFB to Week 12 - 20/12.5 to 20/16	1	0		
CFB to Week 16 - No change	25	27		
CFB to Week 16 - 20/63 to 20/50	0	1		
CFB to Week 16 - 20/50 to 20/40	0	1		
CFB to Week 16 - 20/40 to 20/20	0	1		
CFB to Week 16 - 20/40 to 20/25	1	0		
CFB to Week 16 - 20/40 to 20/32	1	0		
CFB to Week 16 - 20/40 to 20/50	1	0		
CFB to Week 16 - 20/32 to 20/25	2	2		
CFB to Week 16 - 20/25 to 20/16	0	1		
CFB to Week 16 - 20/25 to 20/20	4	0		
CFB to Week 16 - 20/25 to 20/32	0	2		
CFB to Week 16 - 20/20 to 20/16	3	0		
CFB to Week 16 - 20/20 to 20/25	2	2		
CFB to Week 16 - 20/16 to 20/20	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Following study ICF signature, at each visit, after the patient had the opportunity to spontaneously mention any problems, the Investigator or appropriate designee inquired about AEs.

Adverse event reporting additional description:

All AEs were followed-up to determine outcome of the reaction. All ADRs and SAEs ongoing at the time the patient's study participation ended were evaluated within 10 days after the final visit. After this period, all unresolved ADRs and SAEs were reported as "ongoing" in the eCRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Cenegermin

Reporting group description:

Cenegermin (rhNGF 20 mcg/mL)

Reporting group title	Vehicle

Reporting group description:

Placebo vehicle (Vehicle vials). Out of the 41 patients enrolled in the study and assigned to the vehicle treatment group, one patient did not receive any dose of study medication and was therefore excluded from the SAF and FAS populations. Thus, results are reported for the 40 patients in the vehicle group who received treatment.

Serious adverse events	Cenegermin	Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 40 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 4.5 %

Non-serious adverse events	Cenegermin	Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 44 (61.36%)	18 / 40 (45.00%)	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 44 (4.55%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			

Rib fracture			
subjects affected / exposed	2 / 44 (4.55%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 44 (6.82%)	4 / 40 (10.00%)	
occurrences (all)	3	4	
Eye disorders			
Eye discharge			
subjects affected / exposed	2 / 44 (4.55%)	2 / 40 (5.00%)	
occurrences (all)	2	3	
Eye pain			
subjects affected / exposed	21 / 44 (47.73%)	4 / 40 (10.00%)	
occurrences (all)	23	4	
Eyelid pain			
subjects affected / exposed	7 / 44 (15.91%)	0 / 40 (0.00%)	
occurrences (all)	9	0	
Foreign body sensation in eyes			
subjects affected / exposed	0 / 44 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Vision blurred			
subjects affected / exposed	1 / 44 (2.27%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Dry eye			
subjects affected / exposed	0 / 44 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Conjunctival hyperaemia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Eye irritation			
subjects affected / exposed	2 / 44 (4.55%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Photophobia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Swelling of eyelid			

subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	1 / 40 (2.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2021	Amendment 1 (US specific): The purpose of this amendment was to include changes in order to align the Protocol to the version submitted in Italy. Furthermore, minor changes to correct some typos were made.
10 December 2021	Amendment 1 (Italy specific): The purpose of this amendment was to fulfil the requests reported in the AIFA's 'Review Comments' letter dated December 10, 2021.
02 February 2022	Amendment 2: The 'track changes' version highlights the differences from Protocol version 2.0 US Specific to Protocol version 4.0. The purpose of this amendment was to align version numbers as Protocol NGF0221 EU (Version 3.0 Italy specific) and Protocol NGF0221 US (version 2.0 US specific) and to add the study name (PROTEGO-2). Some changes were implemented after specific requests from the Italian Health authorities. Furthermore, minor changes to better explain the study design and to correct some typos were made.
08 February 2022	Amendment 3: The 'track changes' version highlights the differences from Protocol Version No. 3 Italy Specific to Protocol version 4.0. The purpose of this amendment was to align version numbers as Protocol NGF0221 EU (Version 3.0 Italy specific) and Protocol NGF0221 US (version 2.0 US specific) and to add the study name (PROTEGO-2). Furthermore, minor changes to better explain the study design and to correct some typos were made.
16 June 2022	Amendment 4: The purpose of this amendment was to update protocol NGF0221 to shift the key secondary endpoint of SANDE global score to the co-primary endpoint to satisfy the FDA's request. The proposed change aligned with one of the other Phase 3 studies, NGF0121 (PROTEGO-1) – "A 4- week, Phase 3, multicenter, double-masked, vehicle-controlled clinical study to evaluate safety and efficacy of Oxervate (cenegermin) 20 mcg/mL ophthalmic solution versus vehicle, in patients with severe Sjogren's dry eye disease". NGF0121 and NGF0221 were already approved by AIFA and EC/IRB and were then ongoing. Below is the list of substantial revisions made in the Protocol: • Added co-primary efficacy endpoint: change from baseline in SANDE global score at Week 12. (Shifted from secondary to co-primary endpoint) Consequently, • An increase in the sample size from 48 to 80 enrolled patients with a 10% dropout rate resulted in an increase in eligible patients from 42 to 72 patients. •Update to statistical methods to incorporate the above-listed modification. Furthermore, minor changes to correct some typographical errors were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Patients had severe DED and persistent symptoms despite receiving topical CsA. The vehicle response could be due to a lubricating vehicle's effect or a variable response in patients with episodic flare-ups. Also, the treatment duration was short.

Notes: