



Clinical trial results:

A 4-week, Phase III, multicentre, double-masked, vehicle-controlled 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 (PROTEGO-1 study)

Summary

EudraCT number	2021-003346-21
Trial protocol	IT
Global end of trial date	19 December 2022

Results information

Result version number	v1 (current)
This version publication date	19 January 2024
First version publication date	19 January 2024

Trial information

Trial identification

Sponsor protocol code	NGF0121
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05133180
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
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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	13 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2022
Global end of trial reached?	Yes
Global end of trial date	19 December 2022
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).

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 thumbprint 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, administered additional drops and documented 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. 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 for 28 days (four weeks).

Actual start date of recruitment	19 January 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	Italy: 51
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	104
EEA total number of subjects	51

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)	74
From 65 to 84 years	29
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Three sites in Italy and 7 sites in US enrolled patients. A total of 126 patients were assessed for eligibility. There were 22 screening failures. The remaining patients (n=104) were randomized 1:1 as follows: 52 to cenegermin and 52 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) $\geq 2 \leq 5$ mm/5min. BCDVA score ≥ 0.1 decimal units (20/200 Snellen value) in each eye at study enrolment.

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.

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
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Arm description:

Group 2: Placebo vehicle (Vehicle vials). Out of the 52 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 51 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	52	51
Completed	50	49
Not completed	2	2
Consent withdrawn by subject	1	1
Disease progression	-	1
Lost to follow-up	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 104 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 103 patients: 52 patients in the cenegermin group and 51 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 52 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 51 patients in the vehicle group who received treatment.	

Reporting group values	Cenegermin	Vehicle	Total
Number of subjects	52	51	103
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	34	73
From 65-84 years	13	16	29
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	55.3	58.7	
standard deviation	± 13.47	± 14.10	-
Gender categorical			
Units: Subjects			
Female	50	47	97
Male	2	4	6
Geographic region			
Units: Subjects			
Europe	27	23	50
US	25	28	53
Site			
Units: Subjects			
Site #01	10	8	18
Site #02	4	3	7
Site #04	13	12	25
Site #05	7	8	15
Site #06	5	5	10
Site #07	6	8	14
Site #08	0	1	1
Site #09	2	0	2

Site #10	4	5	9
Site #12	1	1	2
Race			
Units: Subjects			
Asian	0	3	3
Black or African American	0	1	1
White	43	39	82
Other	2	0	2
Multiple	1	1	2
Missing	6	7	13
Ethnicity			
Units: Subjects			
Hispanic or Latino	7	5	12
Not Hispanic or Latino	41	39	80
Missing	3	5	8
Not reported	1	2	3

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 52 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 51 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	52	51		
Units: Subjects	19	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 >10mm/5min 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.946

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.412
upper limit	84.165

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	52	51		
Units: Change from baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-29.528 (-42.126 to -16.930)	-24.967 (-37.009 to -12.926)		

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 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322 ^[1]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	-4.561
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.581
upper limit	4.459

Notes:

[1] - Adjusted means difference [95% CI] between the two groups (-4.561 [-13.581; 4.459]) was not statistically significant (p-value=0.322).

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

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

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

End point type	Secondary
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End point timeframe:

Week 8

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Subjects	18	2		

Statistical analyses

Statistical analysis title	Logistic Regression Model
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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 >10mm/5min 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.091
upper limit	82.31

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
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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
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End point timeframe:

Week 12

End point values	Cenegermín	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Change from Baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-31.445 (-43.795 to -19.095)	-26.713 (-38.538 to -14.887)		

Statistical analyses

Statistical analysis title	ANCOVA
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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	Cenegermín v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307 ^[2]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	-4.732
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.819
upper limit	4.354

Notes:

[2] - Adjusted mean change from baseline in the cenegermin group was not statistically significantly superior to that in the vehicle group (p-value=0.307).

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
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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
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End point timeframe:

Week 12

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Change from baseline in SANDE score				
arithmetic mean (confidence interval 95%)	-24.546 (-38.261 to -10.831)	-21.793 (-34.944 to -8.643)		

Statistical analyses

Statistical analysis title	ANCOVA
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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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.572 ^[3]
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	-2.753
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.303
upper limit	6.798

Notes:

[3] - The adjusted means difference between the two groups was not statistically significant (p-value=0.572).

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
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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
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End point timeframe:

Week 12 and Week 4.

End point values	Cenegermín	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Changes from baseline in IDEEL modules				
least squares mean (confidence interval 95%)				
QoL (Daily activities) - Week 4	11.524 (5.207 to 17.842)	9.364 (3.354 to 15.374)		
QoL (Daily activities) - Week 12	13.301 (6.267 to 20.335)	9.223 (2.437 to 16.008)		
QoL (Feelings) - Week 4	14.385 (6.840 to 21.930)	11.955 (4.732 to 19.177)		
QoL (Feelings) - Week 12	16.069 (7.476 to 24.661)	10.519 (2.185 to 18.853)		
QoL (Work) - Week 4	17.591 (8.213 to 26.969)	14.291 (5.787 to 22.795)		
QoL (Work) - Week 12	18.619 (9.309 to 27.928)	15.144 (6.371 to 23.916)		
TS (Treatment - in general) - Week 4	9.505 (2.772 to 16.237)	8.432 (1.840 to 15.025)		
TS (Treatment - in general) - Week 12	6.482 (-0.877 to 13.842)	4.239 (-2.942 to 11.420)		
TS (Treatment - Eye drops) - Week 4	13.879 (2.071 to 25.686)	14.428 (3.246 to 25.609)		
TS (Treatment - Eye drops) - Week 12	12.733 (1.180 to 24.285)	16.938 (5.033 to 28.844)		
Symptom-Bother - Week 4	-10.241 (-16.924 to -3.557)	-9.435 (-15.876 to -2.995)		
Symptom-Bother - Week 12	-16.323 (-23.582 to -9.064)	-7.533 (-14.574 to -0.493)		

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 (MNAR) 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	Cenegermín v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468 ^[4]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	2.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.668
upper limit	7.988

Notes:

[4] - Not statistically significant result.

Statistical analysis title	QoL (Daily activities) - Week 12
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Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.268 ^[5]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	4.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.142
upper limit	11.299

Notes:

[5] - Not statistically significant result.

Statistical analysis title	QoL (Feelings) - Week 4
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Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.492 ^[6]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	2.431
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	9.362

Notes:

[6] - Not statistically significant result.

Statistical analysis title	QoL (Feelings) - Week 12
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227 ^[7]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	5.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.462
upper limit	14.562

Notes:

[7] - Not statistically significant result.

Statistical analysis title	QoL (Work) - Week 4
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51 ^[8]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.511
upper limit	13.111

Notes:

[8] - Not statistically significant result.

Statistical analysis title	QoL (Work) - Week 12
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501 ^[9]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	3.475
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.651
upper limit	13.601

Notes:

[9] - Not statistically significant result.

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

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745 ^[10]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.398
upper limit	7.542

Notes:

[10] - Not statistically significant result.

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

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.564 ^[11]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	2.244

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.387
upper limit	9.874

Notes:

[11] - Not statistically significant result.

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

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.924 ^[12]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.549
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.82
upper limit	10.723

Notes:

[12] - Not statistically significant result.

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

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467 ^[13]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-4.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.53
upper limit	7.118

Notes:

[13] - Not statistically significant result.

Statistical analysis title	Symptom-Bother - Week 4
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802 ^[14]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-0.805
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.086
upper limit	5.476

Notes:

[14] - Not statistically significant result.

Statistical analysis title	Symptom-Bother - Week 12
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-8.789
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.16
upper limit	-1.418

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	52	51		
Units: Change from baseline				
least squares mean (confidence interval 95%)				
Week 4	-4.107 (-5.723 to -2.490)	-2.588 (-4.118 to -1.059)		
Week 8	-4.442 (-6.145 to -2.739)	-2.668 (-4.298 to -1.038)		
Week 12	-3.714 (-5.522 to -1.905)	-2.490 (-4.222 to -0.758)		

Statistical analyses

Statistical analysis title	Week 4
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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. Subject will be considered as a random effect and the covariance matrix used will be unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 ^[15]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-1.518
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.005
upper limit	-0.031

Notes:

[15] - Not statistically significant at the 2.5% level of significance.

Statistical analysis title	Week 8
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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. Subject will be considered as a random effect and the covariance matrix used will be unstructured.

Comparison groups	Cenegermin v Vehicle
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Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038 ^[16]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-1.773
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.446
upper limit	-0.101

Notes:

[16] - Not statistically significant result.

Statistical analysis title	Week 12
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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. Subject will be considered as a random effect and the covariance matrix used will be unstructured.

Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 ^[17]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	-1.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.096
upper limit	0.649

Notes:

[17] - 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
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End point description:

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

End point type	Secondary
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End point timeframe:

Week 4, Week 8 and Week 12.

End point values	Cenegerman	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Change from baseline in TFBUT				
least squares mean (confidence interval 95%)				
Week 4	1.808 (0.437 to 3.178)	0.167 (-1.144 to 1.479)		
Week 8	2.010 (0.579 to 3.441)	0.876 (-0.502 to 2.255)		
Week 12	1.973 (0.588 to 3.358)	0.613 (-0.715 to 1.941)		

Statistical analyses

Statistical analysis title	Week 4
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	Cenegerman v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.98

Statistical analysis title	Week 8
Statistical analysis description:	
Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	Cenegerman v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129 ^[18]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.133

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.329
upper limit	2.596

Notes:

[18] - Not statistically significant at the 2.5% level of significance.

Statistical analysis title	Week 12
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Statistical analysis description:

Analysis is based on MMRM with Multiple Imputation (MI) under missing not at random (MNAR) 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	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 ^[19]
Method	Mixed Model for Repeated Measures
Parameter estimate	LS means difference
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	2.722

Notes:

[19] - Not statistically significant at the 2.5% level of significance.

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
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End point description:

Change from Baseline in Schirmer I Test at each Timepoint.

End point type	Secondary
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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	52 ^[20]	51 ^[21]		
Units: Change from baseline in Schirmer I Test				
arithmetic mean (standard deviation)				
Week 4	5.4 (± 6.6)	0.8 (± 2.7)		
Week 8	4.9 (± 6.6)	1.4 (± 2.9)		
Week 12	3.8 (± 5.2)	1.4 (± 4.1)		

Week 16	3.6 (\pm 5.1)	1.7 (\pm 4.8)		
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Notes:

[20] - Week 4, n=51; Week 8, n=49; Week 12, n=49; Week 16, n=50.

[21] - Week 4, n=50; Week 8, n=49; Week 12, n=49; Week 16, n=49.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	< 0.001 ^[23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[23] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	= 0.009 ^[25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - 103 subjects are included in the FAS, however only 98 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 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.02 ^[27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - 103 subjects are included in the FAS, however only 98 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 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.022 ^[29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - 103 subjects are included in the FAS, however only 99 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

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
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End point description:

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

End point type	Secondary
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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	52 ^[30]	51 ^[31]		
Units: Change from baseline in NEI scale				
arithmetic mean (standard deviation)				
Week 4	-3.1 (± 5.0)	-2.0 (± 2.8)		
Week 8	-3.5 (± 5.0)	-2.1 (± 3.8)		
Week 12	-2.7 (± 5.6)	-2.0 (± 4.0)		
Week 16	-3.3 (± 4.6)	-2.7 (± 5.8)		

Notes:

[30] - Week 4, n=51; Week 8, n=49; Week 12, n=49; Week 16, n=50.

[31] - Week 4, n=50; Week 8, n=49; Week 12, n=49; Week 16, n=49.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.117 ^[33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[32] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[33] - 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 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.095 ^[35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[35] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.217 ^[37]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - 103 subjects are included in the FAS, however only 98 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 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[38]
P-value	= 0.065 ^[39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - 103 subjects are included in the FAS, however only 99 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.

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	52 ^[40]	51 ^[41]		
Units: Change from baseline in TFBUT arithmetic mean (standard deviation)				
Week 4	1.7 (± 4.2)	0.1 (± 2.6)		
Week 8	2.0 (± 4.4)	0.8 (± 3.1)		
Week 12	1.9 (± 4.1)	0.6 (± 2.9)		
Week 16	1.3 (± 3.1)	0.4 (± 2.8)		

Notes:

[40] - Week 4, n=51; Week 8, n=49; Week 12, n=49; Week 16, n=50.

[41] - Week 4, n=50; Week 8, n=49; Week 12, n=49; Week 16, n=49.

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	Vehicle v Cenegermin
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	= 0.031 ^[43]
Method	Wilcoxon (Mann-Whitney)

Notes:

[42] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[43] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[44]
P-value	= 0.273 ^[45]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - 103 subjects are included in the FAS, however only 98 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 Vehicle in all patients.

Statistical analysis title	Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[46]
P-value	= 0.072 ^[47]
Method	Wilcoxon (Mann-Whitney)

Notes:

[46] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[47] - 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
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Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	= 0.125 ^[49]
Method	Wilcoxon (Mann-Whitney)

Notes:

[48] - 103 subjects are included in the FAS, however only 99 subjects are analyzed in this table due to the presence of missing values.

[49] - 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 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
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End point description:

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

End point type	Secondary
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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	52 ^[50]	51 ^[51]		
Units: Change from baseline in SANDE scores				
arithmetic mean (standard deviation)				
Global Score - Week 8	-26.0 (± 20.1)	-15.2 (± 22.1)		
Global Score - Week 12	-20.4 (± 22.0)	-15.7 (± 26.7)		
Global Score - Week 16	-15.2 (± 20.5)	-16.0 (± 25.2)		
Severity - Week 8	-23.7 (± 20.8)	-14.4 (± 21.6)		
Severity - Week 12	-21.2 (± 23.5)	-15.7 (± 26.5)		
Severity - Week 16	-16.6 (± 23.6)	-16.1 (± 25.9)		
Frequency - Week 8	-27.1 (± 22.5)	-15.9 (± 24.4)		
Frequency - Week 12	-17.9 (± 23.4)	-15.7 (± 28.2)		
Frequency - Week 16	-12.5 (± 21.2)	-16.1 (± 25.6)		

Notes:

[50] - Week 8, n=49; Week 12, n=49; Week 16, n=50.

[51] - Week 8, n=49; Week 12, n=49; Week 16, n=49.

Statistical analyses

Statistical analysis title	Global Score - Week 8
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[52]
P-value	= 0.005 ^[53]
Method	Wilcoxon (Mann-Whitney)

Notes:

[52] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[53] - 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 - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[54]
P-value	= 0.116 ^[55]
Method	Wilcoxon (Mann-Whitney)

Notes:

[54] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[55] - 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	Global Score - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[56]
P-value	= 0.864 ^[57]
Method	Wilcoxon (Mann-Whitney)

Notes:

[56] - 103 subjects are included in the FAS, however only 99 subjects are analyzed in this table due to the presence of missing values.

[57] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[58]
P-value	= 0.016 ^[59]
Method	Wilcoxon (Mann-Whitney)

Notes:

[58] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[59] - 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 12
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[60]
P-value	= 0.16 ^[61]
Method	Wilcoxon (Mann-Whitney)

Notes:

[60] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[61] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[62]
P-value	= 0.839 ^[63]
Method	Wilcoxon (Mann-Whitney)

Notes:

[62] - 103 subjects are included in the FAS, however only 99 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	Frequency - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[64]
P-value	= 0.011 ^[65]
Method	Wilcoxon (Mann-Whitney)

Notes:

[64] - 103 subjects are included in the FAS, however only 98 subjects are analyzed in this table due to the presence of missing values.

[65] - 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[66]
P-value	= 0.316 ^[67]
Method	Wilcoxon (Mann-Whitney)

Notes:

[66] - 103 subjects are included in the FAS, however only 98 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 16
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[68]
P-value	= 0.685 ^[69]
Method	Wilcoxon (Mann-Whitney)

Notes:

[68] - 103 subjects are included in the FAS, however only 99 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.

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

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

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

End point type	Secondary
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End point timeframe:

Week 4.

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 ^[70]	51 ^[71]		
Units: Subjects				
Worsening in symptom scores (SANDE global score)	4	11		
NEI score \geq 50%	1	0		
Worsening in symptom scores and/or NEI score \geq 50	4	11		

Notes:

[70] - Week 4, n=51

[71] - Week 4, n=50

Statistical analyses

Statistical analysis title	Worsening in symptom scores (SANDE global score)
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[72]
P-value	= 0.0455 ^[73]
Method	Chi-squared

Notes:

[72] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[73] - p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients

Statistical analysis title	NEI score \geq 50%
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[74]
P-value	= 1 ^[75]
Method	Fisher exact

Notes:

[74] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[75] - Not statistically significant result. p-value corresponds to 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[76]
P-value	= 0.0455 ^[77]
Method	Chi-squared

Notes:

[76] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[77] - 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
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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
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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	52	51		
Units: Change from baseline in IDEEL score				
arithmetic mean (standard deviation)				
QoL (Impact on Daily Activities) - Week 4	12.1 (± 18.5)	7.8 (± 18.4)		
QoL (Impact on Daily Activities) - Week 8	14.6 (± 18.8)	6.5 (± 23.2)		
QoL (Impact on Daily Activities) - Week 12	14.7 (± 19.2)	7.2 (± 22.8)		
QoL (Impact on Daily Activities) - Week 16	15.1 (± 20.8)	9.7 (± 21.1)		
QoL (Emotional Impact due to Dry Eye) - Week 4	15.6 (± 22.6)	10.7 (± 16.9)		
QoL (Emotional Impact due to Dry Eye) - Week 8	18.4 (± 21.9)	10.3 (± 22.9)		
QoL (Emotional Impact due to Dry Eye) - Week 12	17.9 (± 24.5)	8.9 (± 24.4)		

QoL (Emotional Impact due to Dry Eye) - Week 16	19.0 (± 23.1)	11.5 (± 23.3)		
QoL (Impact on Work due to Dry Eye) - Week 4	18.8 (± 22.8)	8.0 (± 19.8)		
QoL (Impact on Work due to Dry Eye) - Week 8	17.7 (± 25.7)	9.5 (± 25.9)		
QoL (Impact on Work due to Dry Eye) - Week 12	19.1 (± 21.1)	8.2 (± 21.2)		
QoL (Impact on Work due to Dry Eye) - Week 16	20.9 (± 24.2)	9.3 (± 26.7)		
TS (Satisfaction with Effectiveness) - Week 4	17.8 (± 35.4)	3.4 (± 36.5)		
TS (Satisfaction with Effectiveness) - Week 8	17.7 (± 31.0)	7.7 (± 36.4)		
TS (Satisfaction with Effectiveness) - Week 12	15.2 (± 28.4)	7.2 (± 36.7)		
TS (Satisfaction with Effectiveness) - Week 16	13.4 (± 28.7)	1.2 (± 35.9)		
TS (Treatment Bother/Inconvenience) - Week 4	16.3 (± 22.2)	4.9 (± 25.6)		
TS (Treatment Bother/Inconvenience) - Week 8	16.6 (± 21.1)	2.7 (± 28.1)		
TS (Treatment Bother/Inconvenience) - Week 12	13.6 (± 25.0)	3.2 (± 28.0)		
TS (Treatment Bother/Inconvenience) - Week 16	13.3 (± 23.6)	5.3 (± 27.3)		
Symptom-Bother - Week 4	-13.9 (± 18.9)	-10.3 (± 19.3)		
Symptom-Bother - Week 8	-19.5 (± 20.3)	-6.9 (± 19.2)		
Symptom-Bother - Week 12	-20.7 (± 20.1)	-8.3 (± 22.2)		
Symptom-Bother - Week 16	-18.6 (± 19.4)	-11.1 (± 22.3)		

Statistical analyses

Statistical analysis title	QoL (Impact on Daily Activities) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[78]
P-value	= 0.202 ^[79]
Method	Wilcoxon (Mann-Whitney)

Notes:

[78] - 103 subjects are included in the FAS, however only 101 subjects (Cenegermin, n=51; Vehicle, n=50) are analyzed in this table due to the presence of missing values.

[79] - 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 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[80]
P-value	= 0.06 ^[81]
Method	t-test, 2-sided

Notes:

[80] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[81] - 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	QoL (Impact on Daily Activities) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[82]
P-value	= 0.082 ^[83]
Method	t-test, 2-sided

Notes:

[82] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[83] - 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	QoL (Impact on Daily Activities) - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[84]
P-value	= 0.203 ^[85]
Method	t-test, 2-sided

Notes:

[84] - 103 subjects are included in the FAS, however only 99 (Cenegermin, n=50; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[85] - 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	QoL (Emotional Impact due to Dry Eye) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[86]
P-value	= 0.219 ^[87]
Method	t-test, 2-sided

Notes:

[86] - 103 subjects are included in the FAS, however only 101 (Cenegermin, n=51; Vehicle, n=50) subjects are analyzed in this table due to the presence of missing values.

[87] - 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	QoL (Emotional Impact due to Dry Eye) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[88]
P-value	= 0.079 ^[89]
Method	t-test, 2-sided

Notes:

[88] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[89] - 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	QoL (Emotional Impact due to Dry Eye) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[90]
P-value	= 0.07 ^[91]
Method	t-test, 2-sided

Notes:

[90] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[91] - 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	QoL (Emotional Impact due to Dry Eye) - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[92]
P-value	= 0.114 ^[93]
Method	t-test, 2-sided

Notes:

[92] - 103 subjects are included in the FAS, however only 99 (Cenegermin, n=50; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[93] - 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	QoL (Impact on Work due to Dry Eye) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[94]
P-value	= 0.069 ^[95]
Method	t-test, 2-sided

Notes:

[94] - 103 subjects are included in the FAS, however only 54 (Cenegermin, n=24; Vehicle, n=30) subjects are analyzed in this table due to the presence of missing values.

[95] - 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	QoL (Impact on Work due to Dry Eye) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[96]
P-value	= 0.251 ^[97]
Method	t-test, 2-sided

Notes:

[96] - 103 subjects are included in the FAS, however only 54 (Cenegermin, n=24; Vehicle, n=30) subjects are analyzed in this table due to the presence of missing values.

[97] - 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	QoL (Impact on Work due to Dry Eye) - Week 12
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[98]
P-value	= 0.073 ^[99]
Method	t-test, 2-sided

Notes:

[98] - 103 subjects are included in the FAS, however only 51 (Cenegermin, n=23; Vehicle, n=28) subjects are analyzed in this table due to the presence of missing values.

[99] - 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	QoL (Impact on Work due to Dry Eye) - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[100]
P-value	= 0.112 ^[101]
Method	t-test, 2-sided

Notes:

[100] - 103 subjects are included in the FAS, however only 52 (Cenegermin, n=23; Vehicle, n=29) subjects are analyzed in this table due to the presence of missing values.

[101] - 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	TS (Satisfaction with Effectiveness) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[102]
P-value	= 0.058 ^[103]
Method	t-test, 2-sided

Notes:

[102] - 103 subjects are included in the FAS, however only 92 (Cenegermin, n=48; Vehicle, n=44) subjects are analyzed in this table due to the presence of missing values.

[103] - 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	TS (Satisfaction with Effectiveness) - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[104]
P-value	= 0.16 ^[105]
Method	t-test, 2-sided

Notes:

[104] - 103 subjects are included in the FAS, however only 91 (Cenegermin, n=47; Vehicle, n=44) subjects are analyzed in this table due to the presence of missing values.

[105] - 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	TS (Satisfaction with Effectiveness) - Week 12
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[106]
P-value	= 0.243 ^[107]
Method	t-test, 2-sided

Notes:

[106] - 103 subjects are included in the FAS, however only 92 (Cenegermin, n=48; Vehicle, n=44) subjects are analyzed in this table due to the presence of missing values.

[107] - 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	TS (Satisfaction with Effectiveness) - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[108]
P-value	= 0.076 ^[109]
Method	t-test, 2-sided

Notes:

[108] - 103 subjects are included in the FAS, however only 90 (Cenegermin, n=48; Vehicle, n=42) subjects are analyzed in this table due to the presence of missing values.

[109] - 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	TS (Treatment Bother/Inconvenience) - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[110]
P-value	= 0.025 ^[111]
Method	t-test, 2-sided

Notes:

[110] - 103 subjects are included in the FAS, however only 92 (Cenegermin, n=48; Vehicle, n=44) subjects are analyzed in this table due to the presence of missing values.

[111] - p-value corresponds to two sample (independent group) t-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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[112]
P-value	= 0.009 ^[113]
Method	t-test, 2-sided

Notes:

[112] - 103 subjects are included in the FAS, however only 92 (Cenegermin, n=46; Vehicle, n=46) subjects are analyzed in this table due to the presence of missing values.

[113] - p-value corresponds to two sample (independent group) t-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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[114]
P-value	= 0.063 ^[115]
Method	t-test, 2-sided

Notes:

[114] - 103 subjects are included in the FAS, however only 93 (Cenegermin, n=47; Vehicle, n=46) subjects are analyzed in this table due to the presence of missing values.

[115] - 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	TS (Treatment Bother/Inconvenience) - Week 16
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[116]
P-value	= 0.128 ^[117]
Method	t-test, 2-sided

Notes:

[116] - 103 subjects are included in the FAS, however only 94 (Cenegermin, n=48; Vehicle, n=46) subjects are analyzed in this table due to the presence of missing values.

[117] - 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	Symptom-Bother - Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[118]
P-value	= 0.349 ^[119]
Method	t-test, 2-sided

Notes:

[118] - 103 subjects are included in the FAS, however only 101 (Cenegermin, n=51; Vehicle, n=50) subjects are analyzed in this table due to the presence of missing values.

[119] - 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	Symptom-Bother - Week 8
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[120]
P-value	= 0.002 ^[121]
Method	t-test, 2-sided

Notes:

[120] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[121] - p-value corresponds to 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[122]
P-value	= 0.005 ^[123]
Method	t-test, 2-sided

Notes:

[122] - 103 subjects are included in the FAS, however only 98 (Cenegermin, n=49; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

[123] - p-value corresponds to 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	103
Analysis specification	Pre-specified
Analysis type	superiority ^[124]
P-value	= 0.076 ^[125]
Method	t-test, 2-sided

Notes:

[124] - 103 subjects are included in the FAS, however only 99 (Cenegermin, n=50; Vehicle, n=49) subjects are analyzed in this table due to the presence of missing values.

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

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

End point title	Proportion and Frequency of Preservative Free Artificial Tears Use (n° drops/day)
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End point description:

Use of Preservative Free Artificial Tears by Study Period

End point type	Other pre-specified
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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	52 ^[126]	51 ^[127]		
Units: Preservative Free Artificial Tears				
arithmetic mean (standard deviation)				
Treatment Period	298.6 (± 443.5)	195.0 (± 174.8)		
Follow-up Period	364.5 (± 366.6)	284.8 (± 187.9)		
Overall	331.9 (± 405.6)	242.5 (± 186.3)		

Notes:

[126] - Treatment period, n=46; Follow-up period, n=47; Overall, n=49

[127] - Treatment period, n=40; Follow-up period, n=45; Overall, n=49

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:	
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	52 ^[128]	51 ^[129]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	4.1 (± 5.6)	0.8 (± 3.4)		

Notes:

[128] - N=50

[129] - N=51

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[130]
P-value	< 0.001 ^[131]
Method	Wilcoxon (Mann-Whitney)

Notes:

[130] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[131] - 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:	
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	52 ^[132]	51 ^[133]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	-2.7 (± 4.2)	-1.6 (± 3.4)		

Notes:

[132] - N=50

[133] - N=51

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[134]
P-value	= 0.038 ^[135]
Method	Wilcoxon (Mann-Whitney)

Notes:

[134] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[135] - 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 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
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End point description:

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	52 ^[136]	51 ^[137]		
Units: Change from baseline to Week 2				
arithmetic mean (standard deviation)	1.2 (± 3.4)	0.1 (± 2.4)		

Notes:

[136] - N=50

[137] - N=51

Statistical analyses

Statistical analysis title	Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[138]
P-value	= 0.023 ^[139]
Method	Wilcoxon (Mann-Whitney)

Notes:

[138] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[139] - 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 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
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End point description:

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	52 ^[140]	51 ^[141]		
Units: Change from baseline				
arithmetic mean (standard deviation)				
Global Score - Change from baseline to Week 2	-13.9 (± 19.9)	-14.7 (± 21.7)		
Global Score - Change from baseline to Week 4	-18.8 (± 20.9)	-17.4 (± 22.8)		
Severity - Change from baseline to Week 2	-13.3 (± 21.9)	-13.9 (± 21.2)		
Severity - Change from baseline to Week 4	-17.8 (± 23.0)	-16.6 (± 23.1)		
Frequency - Change from baseline to Week 2	-13.8 (± 21.2)	-15.4 (± 23.8)		
Frequency - Change from baseline to Week 4	-19.3 (± 22.3)	-18.0 (± 24.6)		

Notes:

[140] - Week 2, n=50; Week 4, n=51.

[141] - Week 2, n=51; Week 4, n=50.

Statistical analyses

Statistical analysis title	Global Score - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[142]
P-value	= 0.954 ^[143]
Method	Wilcoxon (Mann-Whitney)

Notes:

[142] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[143] - 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 participants

Statistical analysis title	Global Score - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[144]
P-value	= 0.752 ^[145]
Method	t-test, 2-sided

Notes:

[144] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

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

Statistical analysis title	Severity - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[146]
P-value	= 0.817 ^[147]
Method	Wilcoxon (Mann-Whitney)

Notes:

[146] - 103 subjects are included in the FAS, however only 101 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 participants

Statistical analysis title	Severity - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[148]
P-value	= 0.552 ^[149]
Method	Wilcoxon (Mann-Whitney)

Notes:

[148] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[149] - 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 participants

Statistical analysis title	Frequency - Change from baseline to Week 2
Comparison groups	Cenegermin v Vehicle

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[150]
P-value	= 0.651 ^[151]
Method	Wilcoxon (Mann-Whitney)

Notes:

[150] - 103 subjects are included in the FAS, however only 101 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 participants

Statistical analysis title	Frequency - Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[152]
P-value	= 0.521 ^[153]
Method	Wilcoxon (Mann-Whitney)

Notes:

[152] - 103 subjects are included in the FAS, however only 101 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 participants

Other pre-specified: Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score \geq 50% assessed at Week 2

End point title	Number of Patients experienced a Worsening in Symptom Scores (SANDE Global Score) and/or NEI Score \geq 50% assessed at Week 2
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End point description:

End point type	Other pre-specified
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End point timeframe:

Week 2

End point values	Cenegermin	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 ^[154]	51 ^[155]		
Units: Subjects				
Worsening in symptom scores (SANDE global score)	12	11		
NEI score \geq 50%	1	0		
Worsening in symptom scores and/or NEI score \geq 50	12	11		

Notes:

[154] - Week 2, n=50

[155] - Week 2, n=51

Statistical analyses

Statistical analysis title	Worsening in symptom scores (SANDE global score)
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[156]
P-value	= 0.7708 ^[157]
Method	Chi-squared

Notes:

[156] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[157] - Not statistically significant result. p-value corresponds to Chi-square test of the comparisons between Cenegermin and Vehicle in all patients.

Statistical analysis title	NEI score \geq 50%
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[158]
P-value	= 0.495 ^[159]
Method	Fisher exact

Notes:

[158] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[159] - Not statistically significant result. p-value corresponds to 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 \geq 50
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[160]
P-value	= 0.7708 ^[161]
Method	Chi-squared

Notes:

[160] - 103 subjects are included in the FAS, however only 101 subjects are analyzed in this table due to the presence of missing values.

[161] - Not statistically significant result. 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	52 ^[162]	51 ^[163]		
Units: Change from baseline in Schirmer II test				
arithmetic mean (standard deviation)	3.7 (± 6.2)	0.6 (± 4.6)		

Notes:

[162] - N=51

[163] - N=48

Statistical analyses

Statistical analysis title	Change from baseline to Week 4
Comparison groups	Cenegermin v Vehicle
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[164]
P-value	= 0.002 ^[165]
Method	Wilcoxon (Mann-Whitney)

Notes:

[164] - 103 subjects are included in the FAS, however only 99 subjects are analyzed in this table due to the presence of missing values.

[165] - 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	52	51		
Units: Subjects				
CFB to Week 2 - No change	37	32		
CFB to Week 2 - 20/125 to 20/160	1	0		
CFB to Week 2 - 20/50 to 20/40	1	1		
CFB to Week 2 - 20/40 to 20/32	0	1		
CFB to Week 2 - 20/32 to 20/20	0	1		
CFB to Week 2 - 20/32 to 20/25	4	4		
CFB to Week 2 - 20/25 to 20/16	0	1		
CFB to Week 2 - 20/25 to 20/20	3	1		
CFB to Week 2 - 20/25 to 20/40	0	2		
CFB to Week 2 - 20/20 to 20/16	0	3		
CFB to Week 2 - 20/20 to 20/25	0	3		

CFB to Week 2 - 20/20 to 20/32	1	1		
CFB to Week 2 - 20/16 to 20/20	3	1		
CFB to Week 4 - No change	36	37		
CFB to Week 4 - 20/125 to 20/160	1	0		
CFB to Week 4 - 20/50 to 20/40	1	1		
CFB to Week 4 - 20/40 to 20/32	1	0		
CFB to Week 4 - 20/32 to 20/20	1	2		
CFB to Week 4 - 20/32 to 20/25	1	1		
CFB to Week 4 - 20/32 to 20/40	0	1		
CFB to Week 4 - 20/25 to 20/20	4	4		
CFB to Week 4 - 20/25 to 20/32	1	1		
CFB to Week 4 - 20/20 to 20/25	1	1		
CFB to Week 4 - 20/20 to 20/32	0	1		
CFB to Week 4 - 20/20 to 20/40	1	0		
CFB to Week 4 - 20/16 to 20/20	3	1		
CFB to Week 8 - No change	35	27		
CFB to Week 8 - 20/125 to 20/200	1	0		
CFB to Week 8 - 20/50 to 20/32	1	0		
CFB to Week 8 - 20/50 to 20/40	0	1		
CFB to Week 8 - 20/40 to 20/32	1	0		
CFB to Week 8 - 20/32 to 20/25	3	3		
CFB to Week 8 - 20/25 to 20/16	1	1		
CFB to Week 8 - 20/25 to 20/20	3	4		
CFB to Week 8 - 20/25 to 20/32	0	2		
CFB to Week 8 - 20/20 to 20/16	0	4		
CFB to Week 8 - 20/20 to 20/25	0	5		
CFB to Week 8 - 20/20 to 20/32	2	0		
CFB to Week 8 - 20/16 to 20/20	2	2		
CFB to Week 12 - No change	38	29		
CFB to Week 12 - 20/125 to 20/320	1	0		
CFB to Week 12 - 20/50 to 20/40	1	1		
CFB to Week 12 - 20/32 to 20/20	0	3		
CFB to Week 12 - 20/32 to 20/25	3	2		
CFB to Week 12 - 20/25 to 20/16	1	0		
CFB to Week 12 - 20/25 to 20/20	2	2		
CFB to Week 12 - 20/25 to 20/32	1	2		
CFB to Week 12 - 20/20 to 20/16	0	3		
CFB to Week 12 - 20/20 to 20/25	0	4		
CFB to Week 12 - 20/20 to 20/32	1	1		
CFB to Week 12 - 20/16 to 20/20	0	1		
CFB to Week 12 - 20/16 to 20/25	1	1		
CFB to Week 16 - No change	36	33		
CFB to Week 16 - 20/125 to 20/250	1	0		
CFB to Week 16 - 20/80 to 20/63	1	0		
CFB to Week 16 - 20/50 to 20/40	1	1		
CFB to Week 16 - 20/40 to 20/32	1	0		
CFB to Week 16 - 20/32 to 20/20	1	2		
CFB to Week 16 - 20/32 to 20/25	1	2		
CFB to Week 16 - 20/25 to 20/16	0	1		
CFB to Week 16 - 20/25 to 20/20	4	2		
CFB to Week 16 - 20/20 to 20/16	0	2		
CFB to Week 16 - 20/20 to 20/25	1	4		

CFB to Week 16 - 20/20 to 20/32	1	1		
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 has 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Cenegermin
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Reporting group description:

Group 1: Cenegermin (rhNGF 20 mcg/mL)

Reporting group title	Vehicle
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Reporting group description:

Group 2: Placebo vehicle (Vehicle vials)

Serious adverse events	Cenegermin	Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 52 (3.85%)	1 / 51 (1.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminaemia			

subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cenegermín	Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 52 (71.15%)	15 / 51 (29.41%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 52 (5.77%)	2 / 51 (3.92%)	
occurrences (all)	3	3	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 52 (5.77%)	1 / 51 (1.96%)	
occurrences (all)	4	2	
Eye discharge			
subjects affected / exposed	2 / 52 (3.85%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Eye irritation			
subjects affected / exposed	1 / 52 (1.92%)	3 / 51 (5.88%)	
occurrences (all)	4	4	
Eye pain			

subjects affected / exposed	25 / 52 (48.08%)	5 / 51 (9.80%)	
occurrences (all)	31	5	
Eye pruritus			
subjects affected / exposed	1 / 52 (1.92%)	5 / 51 (9.80%)	
occurrences (all)	1	7	
Eyelid pain			
subjects affected / exposed	11 / 52 (21.15%)	0 / 51 (0.00%)	
occurrences (all)	16	0	
Foreign body sensation in eyes			
subjects affected / exposed	2 / 52 (3.85%)	4 / 51 (7.84%)	
occurrences (all)	2	4	
Ocular hyperaemia			
subjects affected / exposed	1 / 52 (1.92%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Photophobia			
subjects affected / exposed	4 / 52 (7.69%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Vision blurred			
subjects affected / exposed	4 / 52 (7.69%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 52 (3.85%)	1 / 51 (1.96%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2021	This document amended the Protocol version 2.0 and was included in the Protocol version 4.0. The purpose of this amendment was to fulfil the requests reported in the FDA's "Review Comments" letter dated August 17th, 2021. Furthermore, the amendment included changes in order to align the protocol to the version submitted in Italy.
12 November 2021	This document amended the Protocol version 3.0 and was included in the Protocol version 4.0_Italy specific. The purpose of this amendment was to fulfil the requests reported in the Agenzia Italiana del Farmaco (AIFA)'s "Review Comments" letter dated November 12th, 2021.
18 November 2021	This document amended the Protocol version 4.0_Italy Specific and was included in the Protocol 5.0_Italy Specific. The purpose of this amendment was to fulfil the requests reported in the AIFA's "Review Comments" dated November 18th, 2021.
26 January 2022	This document amended the Protocol version 4.0 and was included in the Protocol Version 6.0. The purpose of this amendment was to align version numbers as Protocol NGF0121 EU (Version 5.0 Italy specific) and US (version 4.0 US specific) and to add the study name (PROTEGO-1). 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.
05 February 2022	This document amended the Protocol Version 5.0_Italy Specific and was included in Protocol Version 6.0. The purpose of this amendment was to align version numbers as Protocol NGF0121 EU (Version 5.0 Italy specific) and US (version 4.0 US specific) and to add the study name (PROTEGO-1). Some changes were implemented after specific requests from FDA. Furthermore, minor changes to better explain the study design and to correct some typos 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 high inflammation level, and cenegermin is not an anti-inflammatory drug. Vehicle response could be due to a beneficial effect of vehicle. The short treatment duration could explain not observed superiority of cenegermin.

Notes: