Clinical trial results:
A 8 weeks, Phase II, single-centre, randomized, double-masked, vehicle-controlled, parallel group study with 4 weeks of follow-up to evaluate preliminary efficacy and safety of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle in patients after cataract and refractive surgery.

Summary

EudraCT number	2016-002172-27
Trial protocol	IT
Global end of trial date	04 September 2017

Results information

Result version number	v1 (current)
This version publication date	16 June 2019
First version publication date	16 June 2019

Trial information

Trial identification

Sponsor protocol code	NGF0116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03035864
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici s.p.a.
Sponsor organisation address	Via Santa Lucia 6, Milan, Italy, 20122
Public contact	CLINICAL DEVELOPMENT, DOMPE' FARMACEUTICI SPA, +39 02583831, info@dompe.com
Scientific contact	CLINICAL DEVELOPMENT, DOMPE' FARMACEUTICI SPA, +39 02583831, info@dompe.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2017
Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess efficacy and safety of rhNGF when administered as eye drops to patients after cataract and refractive surgery.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2017
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: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	173
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 180 patients were screened and all of them were randomized to the assigned treatment: 120 patients were randomised to receive rhNGF and 60 were randomised to receive vehicle.
A total of 160 patients (88.9% of screened patients), 105 (87.5%) in the rhNGF group and 55 (91.7%) in the vehicle group, completed the study.

Pre-assignment

Screening details:

After successful completion of screening, each eligible patient was assigned a consecutive randomisation number from the randomization list (randomization number) according to the sequence of study entry (randomization), from 001 to 180. Drop outs were not to be replaced after randomization.

Period 1

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

Blinding implementation details:

It is a double-masked study

Arms

Are arms mutually exclusive?	Yes
Arm title	rhNGF

Arm description:

rhNGF 20 µg/mL.
One drop (40 µL) corresponding to 0.80 µg of rhNGF was instilled into each eligible eye six times a day (every 2 hours), for a total daily dose of 9.6 µg (both eyes, if applicable), for 56 consecutive days.

Arm type	Experimental
Investigational medicinal product name	rhNGF
Investigational medicinal product code	
Other name	recombinant human nerve growth factor
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Recombinant human Nerve Growth Factor (rhNGF) 20 µg/mL vials.
Dosage: One drop (40 µL) corresponding to 0.80 µg of rhNGF was instilled into each eligible eye (in both eyes, if applicable) six times a day (every 2 hours), for a total daily dose of 9.6 µg (in both eyes, if applicable), for 56 consecutive days. Total dose was 537.6 µg/56 days if both eyes were treated.

Arm title	Vehicle

Arm description:

Vehicle.
One drop (40 µL) was instilled into each eligible eye six times a day (every 2 hours), for 56 consecutive days.

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

Dosage and administration details:

Vehicle vials.

Dosage: One drop (40 µL) was instilled into each eligible eye (in both eyes, if applicable) six times a day (every 2 hours).

Number of subjects in period 1	rhNGF	Vehicle
Started	120	60
Completed	116	59
Not completed	4	1
Consent withdrawn by subject	3	1
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

It is a double-masked study

Arms

Are arms mutually exclusive?	Yes
Arm title	rhNGF

Arm description:

Patients randomized to rhNGF eye drops solution in the 8 weeks treatment period underwent a 4 weeks follow-up period with no further treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Vehicle

Arm description:

Patients randomized to the vehicle in the 8 weeks treatment period underwent a 4 weeks follow-up period with no further treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	rhNGF	Vehicle
Started	116	59
Completed	105	55
Not completed	11	4
Consent withdrawn by subject	3	2
Adverse event, non-fatal	1	-
Lost to follow-up	6	2
Decision unrelated to an adverse event	1	-

Baseline characteristics

Reporting groups	
Reporting group title	rhNGF
Reporting group description:	
rhNGF 20 µg/mL. One drop (40 µL) corresponding to 0.80 µg of rhNGF was instilled into each eligible eye six times a day (every 2 hours), for a total daily dose of 9.6 µg (both eyes, if applicable), for 56 consecutive days.	
Reporting group title	Vehicle
Reporting group description:	
Vehicle. One drop (40 µL) was instilled into each eligible eye six times a day (every 2 hours), for 56 consecutive days.	

Reporting group values	rhNGF	Vehicle	Total
Number of subjects	120	60	180
Age categorical Units: Subjects			
Adults (18-64 years)	115	58	173
From 65-84 years	5	2	7
Gender categorical Units: Subjects			
Female	73	33	106
Male	47	27	74

Subject analysis sets	
Subject analysis set title	rhNGF - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (rhNGF) at the study eye(s).	
Subject analysis set title	Vehicle - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).	
Subject analysis set title	rhNGF - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS): the FAS was defined as all patients in the SAF, who had at least one post-baseline efficacy measurement in a study eye.	
Subject analysis set title	Vehicle - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS): the FAS was defined as all patients in the SAF, who had at least one post-baseline efficacy measurement in a study eye	

Reporting group values	rhNGF - SAF	Vehicle - SAF	rhNGF - FAS
Number of subjects	115	59	112
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Gender categorical Units: Subjects			
Female	71	33	
Male	44	26	

Reporting group values	Vehicle - FAS		
Number of subjects	58		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	rhNGF
Reporting group description:	
rhNGF 20 µg/mL. One drop (40 µL) corresponding to 0.80 µg of rhNGF was instilled into each eligible eye six times a day (every 2 hours), for a total daily dose of 9.6 µg (both eyes, if applicable), for 56 consecutive days.	

Reporting group title	Vehicle
Reporting group description:	
Vehicle. One drop (40 µL) was instilled into each eligible eye six times a day (every 2 hours), for 56 consecutive days.	

Reporting group title	rhNGF
Reporting group description:	
Patients randomized to rhNGF eye drops solution in the 8 weeks treatment period underwent a 4 weeks follow-up period with no further treatment.	

Reporting group title	Vehicle
Reporting group description:	
Patients randomized to the vehicle in the 8 weeks treatment period underwent a 4 weeks follow-up period with no further treatment.	

Subject analysis set title	rhNGF - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (rhNGF) at the study eye(s).	

Subject analysis set title	Vehicle - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).	

Subject analysis set title	rhNGF - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS): the FAS was defined as all patients in the SAF, who had at least one post-baseline efficacy measurement in a study eye.	

Subject analysis set title	Vehicle - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS): the FAS was defined as all patients in the SAF, who had at least one post-baseline efficacy measurement in a study eye	

Primary: Change From Baseline in SANDE Scores for Frequency and Severity Assessed at 8 Weeks of Treatment.

End point title	Change From Baseline in SANDE Scores for Frequency and Severity Assessed at 8 Weeks of Treatment.
End point description:	
The Symptom Assessment in Dry Eye (SANDE) questionnaire is a short questionnaire to evaluate both dry eye intensity and frequency by using a 100 mm visual analogue scale (VAS). The patient symptoms of ocular dryness and/or irritation were quantified on the scale based on two questions that assessed both severity and frequency of symptoms. If at least one SANDE assessment was missing at Week 8, the values of the last post-baseline assessment (including those from unscheduled visits) with non-missing values for frequency and severity were imputed (last observation carried forward, LOCF).	
End point type	Primary

End point timeframe:
Week 8

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	58		
Units: mm				
arithmetic mean (standard deviation)				
Frequency	-37.2 (± 24.85)	-35.7 (± 26.04)		
Severity	-37.8 (± 27.20)	-37.3 (± 20.43)		

Statistical analyses

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Statistical analysis related to "frequency"	
Comparison groups	Vehicle - FAS v rhNGF - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.974
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.85
upper limit	6.63

Notes:

[1] - The comparison between groups will be performed with an exploratory analysis of covariance (ANCOVA) model at a 5% level, considering treatment and eye subgroup (1 vs. 2 study eyes treated) as factors and respective baseline values as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Statistical analysis related to "severity"	
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.399
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.85
upper limit	9.61

Notes:

[2] - The comparison between groups will be performed with an exploratory analysis of covariance (ANCOVA) model at a 5% level, considering treatment and eye subgroup (1 vs. 2 study eyes treated) as factors and respective baseline values as covariate.

Primary: Changes in Corneal Vital Staining With Fluorescein (National Eye Institute [NEI] Scales) at 8 weeks of treatment

End point title	Changes in Corneal Vital Staining With Fluorescein (National Eye Institute [NEI] Scales) at 8 weeks of treatment

End point description:

Corneal Staining was derived as sum of scores of the five corneal sectors (central, superior, inferior nasal and temporal) each of which was scored on a scale of 0–3, with a maximal score of 15.
If at least one assessment was missing at Week 8, the values of the last post-baseline assessment (including those from unscheduled visits) with non-missing values were imputed (last observation carried forward, LOCF).

End point type	Primary

End point timeframe:

Week 8

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	58		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.5 (± 2.11)	-2.2 (± 1.81)		

Statistical analyses

Statistical analysis title	rhNGF vs Vehicle
Comparison groups	Vehicle - FAS v rhNGF - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.214
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.1

Notes:

[3] - The comparison between groups will be performed with an exploratory analysis of covariance (ANCOVA) model at a 5% level, considering treatment and eye subgroup (1 vs. 2 study eyes treated) as factors and respective baseline values as covariate.

Secondary: Changes in Conjunctival Vital Staining With Fluorescein (National Eye Institute [NEI] Scales)

End point title	Changes in Conjunctival Vital Staining With Fluorescein (National Eye Institute [NEI] Scales)

End point description:

Conjunctival Staining was derived as sum of scores of the conjunctival area (nasal-superior paralimbal, nasal-inferior paralimbal, nasal-peripheral, temporal-superior paralimbal, temporal-inferior paralimbal, temporal-peripheral) with a grading scale of 0–3 and with a maximal score of 9 for the nasal and temporal conjunctiva.
Data for the main eye are reported.

End point type	Secondary

End point timeframe:

From baseline to weeks 4, 8 and 12

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[4]	58[5]		
Units: units on a scale				
arithmetic mean (standard deviation)				
week 4	0.0 (± 0.0)	0.0 (± 0.0)		
week 8	0.0 (± 0.0)	0.0 (± 0.0)		
week 12	0.0 (± 0.0)	0.0 (± 0.0)		

Notes:

[4] - Week 4 = 110
Week 8 = 107
Week 12 = 107

[5] - Week 4 = 58
Week 8 = 58
Week 12 = 55

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Tear Film Break-Up Time (TFBUT)

End point title	Changes in Tear Film Break-Up Time (TFBUT)

End point description:

The TFBUT measurement was performed after instillation of 5 microliters of 2% sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. The patient was instructed to blink several times to thoroughly mix the fluorescein with the tear film.
Data for the main eye are reported.

End point type	Secondary

End point timeframe:

From baseline to weeks 4, 8 and 12

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[6]	58[7]		
Units: seconds				
arithmetic mean (standard deviation)				
Week 4	2.5 (± 3.07)	2.5 (± 2.37)		
Week 8	1.9 (± 2.96)	2.2 (± 2.67)		
Week 12	2.3 (± 2.61)	2.7 (± 2.72)		

Notes:

[6] - Week 4 = 110
Week 8 = 107
Week 12 = 107

[7] - Week 4 = 58
Week 8 = 58
Week 12 = 55

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Cochet-Bonnet corneal aesthesiometry

End point title	Changes in Cochet-Bonnet corneal aesthesiometry

End point description:

Corneal sensation was measured in both eyes in each of the four quadrants of the cornea using the Cochet Bonnet aesthesiometer before the instillation of any dilating or anesthetic eye drops.
Data for the main eye are reported.

End point type	Secondary

End point timeframe:

From baseline to week 8

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[8]	58[9]		
Units: cm				
arithmetic mean (standard deviation)				
Superior nasal	-0.1 (± 0.31)	-0.2 (± 0.31)		
Inferior nasal	-0.2 (± 0.32)	-0.1 (± 0.64)		
Superior temporal	-0.2 (± 0.36)	-0.2 (± 0.34)		
Inferior temporal	-0.1 (± 0.41)	0.0 (± 0.64)		

Notes:

[8] - Superior nasal = 107
Inferior nasal = 107
Superior temporal = 107
Inferior temporal = 107

[9] - Superior nasal = 58
Inferior nasal = 58
Superior temporal = 58
Inferior temporal = 58

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SANDE scores (face values) for frequency and severity

End point title	Changes in SANDE scores (face values) for frequency and severity

End point description:

The Symptom Assessment in Dry Eye (SANDE) questionnaire is a short questionnaire to evaluate both dry eye intensity and frequency by using a 100 mm visual analogue scale (VAS). The patient symptoms of ocular dryness and/or irritation were quantified on the scale based on two questions that assessed both severity and frequency of symptoms.

End point type	Secondary

End point timeframe:

From baseline to weeks 4, 8 and 12

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[10]	58[11]		
Units: mm				
arithmetic mean (standard deviation)				
Frequency - week 4	-35.1 (± 22.37)	-33.2 (± 25.18)		
Frequency - week 8	-37.2 (± 24.84)	-35.7 (± 26.04)		
Frequency - week 12	-42.1 (± 22.94)	-38.6 (± 26.25)		
Severity - week 4	-35.7 (± 24.28)	-32.9 (± 20.03)		
Severity - week 8	-37.9 (± 27.51)	-37.3 (± 20.43)		
Severity- week 12	-43.5 (± 22.27)	-38.4 (± 20.23)		

Notes:

[10] - Frequency wk 4 = 110
Fr wk 8 & 12 = 107
Severity wk 4 = 110
Sev wk 8 & 12 = 107

[11] - Frequency Wk 4 & 8 = 58
Fr Wk 12 = 55
Severity Wk 4 & 8 = 58
Sev Wk 12 = 55

Statistical analyses

Statistical analysis title	rhNGF vs Vehicle

Statistical analysis description:

Frequency - week 4

Comparison groups	rhNGF - FAS v Vehicle - FAS

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.881
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.13
upper limit	5.27

Notes:

[12] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Frequency - week 8	
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.926
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.96
upper limit	6.33

Notes:

[13] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Frequency - week 12	
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.426
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.97
upper limit	3.38

Notes:

[14] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Severity - week 4	
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.828
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.04
upper limit	6.29

Notes:

[15] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Severity - week 8	
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.394
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	9.47

Notes:

[16] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Statistical analysis title	rhNGF vs Vehicle
Statistical analysis description:	
Severity - week 12	
Comparison groups	rhNGF - FAS v Vehicle - FAS

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.552
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.41
upper limit	3.44

Notes:

[17] - Analysis results from an Analysis of Covariance (ANCOVA) with Treatment and Number of Study Eyes as factor and Baseline as covariate.

Secondary: Changes from baseline in corneal vital staining with fluorescein (NEI scales) at the other time points

End point title	Changes from baseline in corneal vital staining with fluorescein (NEI scales) at the other time points

End point description:

Corneal Staining was derived as sum of scores of the five corneal sectors (central, superior, inferior nasal and temporal) each of which was scored on a scale of 0–3, with a maximal score of 15.
Data for the main eye are reported.

End point type	Secondary

End point timeframe:

At weeks 4, 12

End point values	rhNGF - FAS	Vehicle - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[18]	58[19]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4	-2.4 (± 2.17)	-2.1 (± 1.85)		
Week 12	-2.5 (± 2.12)	-2.2 (± 1.83)		

Notes:

[18] - n=110 at week 4
n=107 at week 12
[19] - n=55 at week 12

Statistical analyses

Statistical analysis title	rhNGF vs Vehicle at week 4
Comparison groups	Vehicle - FAS v rhNGF - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.487
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.18

Notes:

[20] - The comparison between groups will be performed with an exploratory analysis of covariance (ANCOVA) model at a 5% level, considering treatment and eye subgroup (1 vs. 2 study eyes treated) as factors and respective baseline values as covariate.

Statistical analysis title	RhNGF vs Vehicle at week 12
Comparison groups	rhNGF - FAS v Vehicle - FAS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.593
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.03

Notes:

[21] - The comparison between groups will be performed with an exploratory analysis of covariance (ANCOVA) model at a 5% level, considering treatment and eye subgroup (1 vs. 2 study eyes treated) as factors and respective baseline values as covariate.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
At day 0 (baseline), at weeks 4, 8, and 12 (follow-up visit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	rhNGF - SAF
Reporting group description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (rhNGF) at the study eye(s).	
Reporting group title	Vehicle - SAF
Reporting group description:	
Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).	

Serious adverse events	rhNGF - SAF	Vehicle - SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (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: 0.9 %

Non-serious adverse events	rhNGF - SAF	Vehicle - SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 115 (43.48%)	19 / 59 (32.20%)	
Injury, poisoning and procedural complications			
Eye burns			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Corneal abrasion			

subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 115 (7.83%)	0 / 59 (0.00%)	
occurrences (all)	14	0	
Burning sensation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
DIzziness			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Swelling			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 115 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Eye disorders			
Eye pain			
subjects affected / exposed	23 / 115 (20.00%)	2 / 59 (3.39%)	
occurrences (all)	33	2	
Eye irritation			
subjects affected / exposed	13 / 115 (11.30%)	10 / 59 (16.95%)	
occurrences (all)	21	12	
Vision blurred			
subjects affected / exposed	7 / 115 (6.09%)	10 / 59 (16.95%)	
occurrences (all)	7	12	
Myopia			
subjects affected / exposed	10 / 115 (8.70%)	4 / 59 (6.78%)	
occurrences (all)	10	4	

Dry eye			
subjects affected / exposed	6 / 115 (5.22%)	6 / 59 (10.17%)	
occurrences (all)	8	11	
Eye swelling			
subjects affected / exposed	4 / 115 (3.48%)	2 / 59 (3.39%)	
occurrences (all)	5	2	
Photophobia			
subjects affected / exposed	3 / 115 (2.61%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Eyelid oedema			
subjects affected / exposed	3 / 115 (2.61%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Foreign body sensation in eyes			
subjects affected / exposed	2 / 115 (1.74%)	1 / 59 (1.69%)	
occurrences (all)	2	1	
Visual impairment			
subjects affected / exposed	1 / 115 (0.87%)	1 / 59 (1.69%)	
occurrences (all)	1	2	
Diplopia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Eye pruritus			
subjects affected / exposed	1 / 115 (0.87%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Ocular hyperaemia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Blepharospasm			
subjects affected / exposed	0 / 115 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	2	
Conjunctival irritation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Corneal epithelium defect			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	

Ocular discomfort			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Photopsia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 115 (1.74%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	2 / 115 (1.74%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Rhinalgia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Nasal dryness			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 115 (0.87%)	0 / 59 (0.00%)	
occurrences (all)	1	0	

Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 1 / 115 (0.87%) 1	 0 / 59 (0.00%) 0	
Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	 2 / 115 (1.74%) 3 2 / 115 (1.74%) 2 1 / 115 (0.87%) 1 1 / 115 (0.87%) 1	 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2016	• The use of SANDE scoring system was updated and clarified • The exclusion criterion No. 2 was modified with the specification that particular attention was to be paid to malignancies and neuro-oncological diseases • A pregnancy test was added at Week 4 as per Clinical Trial Facilitation Group (CTFG) guideline • The definition of accepted/forbidden medications was updated • Criteria for study discontinuation were modified with the addition of safety concerns related to IMP • The list of conditions which should not have to be considered, SAEs was modified • Other minor changes or typographical errors correction were performed
12 April 2017	The secondary efficacy endpoint "Changes in Cornea vital staining with fluorescein (NEI scales)" was removed and was modified into a Co-Primary Efficacy Endpoint.

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.

There are no limitations or caveats to this summary of results

Notes: