



Clinical trial results:

An 8-week phase I/II, multicenter, randomized, double-masked, vehicle controlled parallel group study with a 48 or 56 week open-label follow-up period to evaluate the safety and efficacy of two doses (10 µg/ml and 20 µg/ml) of recombinant human nerve growth factor eye drops solution versus vehicle in patients with Stage 2 and 3 of Neurotrophic Keratitis.

Summary

EudraCT number	2012-002527-15
Trial protocol	GB DE PT HU ES PL BE
Global end of trial date	19 May 2016

Results information

Result version number	v2 (current)
This version publication date	15 August 2021
First version publication date	04 June 2017
Version creation reason	• Correction of full data set XML v8 format of the data need to be generated

Trial information

Trial identification

Sponsor protocol code	NGF0212
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dompé Farmaceutici s.p.a.
Sponsor organisation address	via santa Lucia 6, Milano, Italy, 20122
Public contact	Project Development Direction, Dompé Farmaceutici s.p.a., 0039 0258383500, info@dompe.it
Scientific contact	Project Development Direction, Dompé Farmaceutici s.p.a., 0039 0258383500, info@dompe.it

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	19 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2016
Global end of trial reached?	Yes
Global end of trial date	19 May 2016
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 the safety and the efficacy of 2 dose regimens (10 µg/ml or 20 µg/ml 6 times a day) of recombinant human Nerve Growth Factor (rhNGF) eye drops solution compared to vehicle for inducing a complete healing of Stage 2 persistent epithelial defect (PED) and Stage 3 (corneal ulcer) neurotrophic keratitis (NK) as measured by the central reading center evaluating the clinical pictures of corneal fluorescein staining.

Protection of trial subjects:

The clinical study protocol, protocol amendments, informed consent document(s), and any other appropriate study-related documents were reviewed and approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). This study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations, and in compliance with Good Clinical Practice (GCP) guidelines. Informed consent was obtained prior to the conduct of any study-related procedures. The Investigator ensured that all personnel involved in the conduct of the study were qualified to perform their assigned responsibilities through education, training and experience. Any deviations from GCP are described in the report. The consent document met all applicable local laws and provided the patient with information regarding the purpose, procedures, requirements and restrictions of the study, along with any known risks and potential benefits associated with the investigational product and the established provisions for maintaining the confidentiality of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2013
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	Poland: 7
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Italy: 87
Country: Number of subjects enrolled	France: 11
Worldwide total number of subjects	174
EEA total number of subjects	174

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)	97
From 65 to 84 years	68
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The study consisted of 2 periods: an 8-week Phase I/II controlled treatment period and 48/56-week FU period. In the Phase 1 patients were randomized into 2 cohorts (of 9 patients each). In phase 2 patients were randomized in a 1:1:1 ratio (52 patients each group). Data refer to the 1st database lock when the last patient in Phase 2 had completed 12 weeks of FU period

Pre-assignment

Screening details:

The inclusion/exclusion criteria were designed to include individuals 18 years of age or older with Stage 2 (PED) or Stage 3 (corneal ulcer) NK involving only 1 eye and to exclude those with Stage 2 or 3 NK affecting both eyes, any active ocular infection or inflammation not related to NK, or any ocular disease or severe vision loss.

Period 1

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

Blinding implementation details:

During the 8-week randomized, double-masked controlled treatment period, the patient, the Investigator, all other site staff involved in study, and the Sponsor's clinical personnel were blinded to the study treatment. The vials of rhNGF (both doses) and the ones containing the vehicle of rhNGF were identical in appearance and the contents of the vials were indistinguishable. The kit numbers were generated by a SAS programming group. Each kit number was randomly associated with a treatment group.

Arms

Are arms mutually exclusive?	Yes
Arm title	1_rhNGF10_Phase 1_treatment

Arm description:

cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).

Arm type	Experimental
Investigational medicinal product name	rhNGF 10 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

rhNGF 10 µg/ml : one drop 6 times a day (one 35 µl drop equals to 0.35 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	2_rhNGF20_Phase 1_treatment
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Arm description:

cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 20 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	3_vehicle group_Phase 1_treatment
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Arm description:

cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Arm type	Placebo
Investigational medicinal product name	ophthalmic solution of the same composition as the test product without rhNGF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (35 µl each drop) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	4_rhNGF10_Phase 2_treatment
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Arm description:

active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 10 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

rhNGF 10 µg/ml : one drop 6 times a day (one 35 µl drop equals to 0.35 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	5_rhNGF20_Phase 2_treatment
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Arm description:

active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 20 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	6_vehicle group_Phase 2_treatment
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Arm description:

vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Arm type	Placebo
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Investigational medicinal product name	ophthalmic solution of the same composition as the test product without rhNGF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (35 µl each drop) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Number of subjects in period 1	1_rhNGF10_Phase 1_treatment	2_rhNGF20_Phase 1_treatment	3_vehicle group_Phase 1_treatment
Started	7	7	4
Completed	6	6	2
Not completed	1	1	2
Adverse event, serious fatal	-	-	-
withdrawal of consent	-	1	-
Adverse event, non-fatal	1	-	2
other	-	-	-
decision unrelated to adverse event	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	4_rhNGF10_Phase 2_treatment	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment
Started	52	52	52
Completed	45	39	48
Not completed	7	13	4
Adverse event, serious fatal	-	1	-
withdrawal of consent	-	-	-
Adverse event, non-fatal	3	8	1
other	1	2	2
decision unrelated to adverse event	1	1	1
Lack of efficacy	2	1	-

Period 2

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

Blinding implementation details:

During the uncontrolled period, the patient, the Investigator, all other site staff involved in study, and the Sponsor's clinical personnel were blinded to the study treatment. The vials of rhNGF (both doses) and the ones containing the vehicle of rhNGF were identical in appearance and the contents of the vials were indistinguishable. The kit numbers were generated by a SAS programming group. Each kit number was randomly associated with a treatment group.

Arms

Are arms mutually exclusive?	Yes
Arm title	1_rhNGF10_Phase 1_FU

Arm description:

cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).

Arm type	Experimental
Investigational medicinal product name	rhNGF 10 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

rhNGF 10 µg/ml : one drop 6 times a day (one 35 µl drop equals to 0.35 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	2_rhNGF20_Phase 1_FU
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Arm description:

cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 20 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	3_vehicle group_Phase 1_FU
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Arm description:

cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Arm type	Placebo
Investigational medicinal product name	ophthalmic solution of the same composition as the test product without rhNGF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (35 µl each drop) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	4_rhNGF10_Phase 2_FU
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Arm description:

active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 10 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

rhNGF 10 µg/ml : one drop 6 times a day (one 35 µl drop equals to 0.35 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	5_rhNGF20_Phase 2_FU
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Arm description:

active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Arm type	Experimental
Investigational medicinal product name	rhNGF 20 µg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Arm title	6_vehicle group_Phase 2_FU
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Arm description:

vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Arm type	Placebo
Investigational medicinal product name	ophthalmic solution of the same composition as the test product without rhNGF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

one drop 6 times a day (35 µl each drop) according to this scheme: morning (8 AM) Mid-morning (10 AM) Noon (12 PM) Early afternoon (2 PM) Mid afternoon (4 PM) Late afternoon (6 PM)

Number of subjects in period 2	1_rhNGF10_Phase 1_FU	2_rhNGF20_Phase 1_FU	3_vehicle group_Phase 1_FU
Started	6	6	2
Completed	5	5	1
Not completed	1	1	1
Adverse event, serious fatal	-	-	-
Adverse event, non-fatal	1	-	-
still in study after week 20	-	-	-
other	-	-	-
Lost to follow-up	-	-	1

parent withdrew the consent to continue the follow	-	1	-
Lack of efficacy	-	-	-

Number of subjects in period 2	4_rhNGF10_Phase 2_FU	5_rhNGF20_Phase 2_FU	6_vehicle group_Phase 2_FU
Started	45	39	48
Completed	12	13	15
Not completed	33	26	33
Adverse event, serious fatal	5	-	1
Adverse event, non-fatal	-	-	-
still in study after week 20	25	23	25
other	1	3	5
Lost to follow-up	2	-	1
parent withdrew the consent to continue the follow	-	-	-
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	1_rhNGF10_Phase 1_treatment
Reporting group description: cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).	
Reporting group title	2_rhNGF20_Phase 1_treatment
Reporting group description: cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	3_vehicle group_Phase 1_treatment
Reporting group description: cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	
Reporting group title	4_rhNGF10_Phase 2_treatment
Reporting group description: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)	
Reporting group title	5_rhNGF20_Phase 2_treatment
Reporting group description: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	6_vehicle group_Phase 2_treatment
Reporting group description: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	

Reporting group values	1_rhNGF10_Phase 1_treatment	2_rhNGF20_Phase 1_treatment	3_vehicle group_Phase 1_treatment
Number of subjects	7	7	4
Age categorical			
age categorical characteristics are overall described in the trial information section.			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	61.7	52	64.3
standard deviation	± 21.47	± 17.24	± 24.06
Gender categorical			
Units: Subjects			
Female	3	4	2
Male	4	3	2
ethnicity			
ethnicity characteristics			
Units: Subjects			
hispanic, latino or spanish	1	0	0
not hispanic, latino or spanish	6	6	4
NA	0	1	0
race			
race characteristics			

Units: Subjects			
NA	0	1	0
white	7	6	4
black or african	0	0	0
asian	0	0	0

Reporting group values	4_rhNGF10_Phase 2_treatment	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment
Number of subjects	52	52	52
Age categorical			
age categorical characteristics are overall described in the trial information section.			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59	62.5	60.4
standard deviation	± 17.17	± 14.01	± 16.78
Gender categorical			
Units: Subjects			
Female	30	30	35
Male	22	22	17
ethnicity			
ethnicity characteristics			
Units: Subjects			
hispanic, latino or spanish	6	9	5
not hispanic, latino or spanish	42	42	41
NA	4	1	6
race			
race characteristics			
Units: Subjects			
NA	5	1	5
white	46	51	45
black or african	0	0	1
asian	1	0	1

Reporting group values	Total		
Number of subjects	174		
Age categorical			
age categorical characteristics are overall described in the trial information section.			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	104		
Male	70		

ethnicity			
ethnicity characteristics			
Units: Subjects			
hispanic, latino or spanish	21		
not hispanic, latino or spanish	141		
NA	12		
race			
race characteristics			
Units: Subjects			
NA	12		
white	159		
black or african	1		
asian	2		

End points

End points reporting groups

Reporting group title	1_rhNGF10_Phase 1_treatment
Reporting group description: cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).	
Reporting group title	2_rhNGF20_Phase 1_treatment
Reporting group description: cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	3_vehicle group_Phase 1_treatment
Reporting group description: cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	
Reporting group title	4_rhNGF10_Phase 2_treatment
Reporting group description: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)	
Reporting group title	5_rhNGF20_Phase 2_treatment
Reporting group description: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	6_vehicle group_Phase 2_treatment
Reporting group description: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	
Reporting group title	1_rhNGF10_Phase 1_FU
Reporting group description: cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).	
Reporting group title	2_rhNGF20_Phase 1_FU
Reporting group description: cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	3_vehicle group_Phase 1_FU
Reporting group description: cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	
Reporting group title	4_rhNGF10_Phase 2_FU
Reporting group description: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)	
Reporting group title	5_rhNGF20_Phase 2_FU
Reporting group description: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)	
Reporting group title	6_vehicle group_Phase 2_FU
Reporting group description: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period	

Primary: percentage of patient experiencing complete healing at week 4 by central reading

End point title	percentage of patient experiencing complete healing at week 4 by central reading ^[1]
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End point description:

The primary efficacy variable was defined as complete healing of the PED or corneal ulcer measured using corneal fluorescein staining by the central reading center evaluating the clinical pictures. The primary efficacy endpoint was the percentage of patients experiencing complete healing, defined as the greatest diameter of the corneal fluorescein staining in the area of the PED or corneal ulcer, as determined by the reading center, being less than 0.5 mm at the Week 4 visit. An observed case analysis for complete healing at Week 4 was also conducted.

End point type	Primary
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End point timeframe:

evaluation is about the complete healing at week 4 visit,

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is evaluated only for the selected group: all the available results have been reported.

End point values	4_rhNGF10_Phase 2_treatment	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	52	
Units: percentage				
yes	55	58	20	
no	45	42	80	

Statistical analyses

Statistical analysis title	Complete Healing at Week 4_rhNGF10 vs veich
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Statistical analysis description:

Primary Efficacy Analysis of Percentage of Patients who Achieved Complete Healing at Week 4 (LOCF) as Determined by the Reading Center.
Comparison between rhNGF10 and veichle

Comparison groups	4_rhNGF10_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	35.3
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	15.88
upper limit	54.71

Statistical analysis title	Complete Healing at Week 4_rhNGF20 vs veich
Comparison groups	5_rhNGF20_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	38.4
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	18.96
upper limit	57.83

Primary: Adverse events

End point title	Adverse events ^[2]
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End point description:

AEs, SAEs and ADRs were collected throughout the study .Results for specific adverse event categories are reported in the "adverse event" section. Results report the percentage of patients that reported an Adverse event (both serious and not) during the considered period (week 8 and week 20): percentage of patients reported in the FU period (period 2) take into account also the percentage of patient results from treatment period (period 1). Whole Adverse events (also AEs after 12 weeks Follow Up, described in the CSR Addendum Report) are attached. No relapses are occurred during the FU period: in any case all the AE tables are attached.

End point type	Primary
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End point timeframe:

period 1 (8 weeks) and 2 (Follow Up period of 12 weeks, untill week 20)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Available results were reported, but no statistical analyses have been done.

End point values	1_rhNGF10_Phase 1_treatment	1_rhNGF10_Phase 1_FU	2_rhNGF20_Phase 1_treatment	2_rhNGF20_Phase 1_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: 0-100%	43	57	71	29

End point values	3_vehicle group_Phase 1_treatment	3_vehicle group_Phase 1_FU	4_rhNGF10_Phase 2_treatment	4_rhNGF10_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	52	45
Units: 0-100%	100	50	44	36

End point values	5_rhNGF20_Phase 2_treatment	5_rhNGF20_Phase 2_FU	6_vehicle group_Phase 2_treatment	6_vehicle group_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	39	52	48
Units: 0-100%	52	26	39	31

Attachments (see zip file)	16.2.7.1.a Adverse Events_Phase 1.pdf 16.2.7.1.b Adverse Events_Phase 2/16.2.7.1.b Adverse 14.3.1.1.a Adverse Events Overall_Phase 1.pdf 14.3.1.1.b Adverse Events Overall_Phase 2.pdf 14.3.1.2.a Adverse Events per SOC_Phase 1.pdf 14.3.1.2.b Adverse Events per SOC_Phase 2.pdf 14.3.1.5.a Adverse Events treatment related_Phase 1.pdf 14.3.1.5.b Adverse Events treatment related_Phase 2.pdf 14.3.1.6.a Serious Adverse Events_Phase 1.pdf 14.3.1.6.b Serious Adverse Events_Phase 1.pdf 14.3.2.3.a Adverse Events leading to death_Phase 1.pdf 14.3.2.3.b Adverse Events leading to death_Phase 2.pdf 14.3.1.1c Summary of AE _CSR Addendum.pdf 14.3.1.2c Summary of AE by SOC _CSR Addendum.pdf 14.3.1.5c Summary of Treatment Related AE _CSR Addendum. 14.3.1.6c Serious Adverse Events _CSR Addendum.pdf 14.3.2.3c Adverse Events Leading to death _CSR Addendum. 16.2.7.1c AE.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients experiencing complete healing at week 4 by investigator

End point title	Percentage of patients experiencing complete healing at week 4 by investigator ^[3]
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End point description:

Percentage of patients experiencing complete healing of the PED or corneal ulcer determined by corneal fluorescein staining at 4 weeks as defined by the Investigator

End point type	Secondary
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End point timeframe:

analysis conducted at 4 weeks

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is evaluated only for the selected group : all the available results have been reported.

End point values	4_rhNGF10_Phase 2_treatment	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	52	
Units: percentage				
yes	52	61	26	
no	48	39	74	

Statistical analyses

Statistical analysis title	Complete Healing at Week 4_rhNGF10 vs veich
Statistical analysis description: by investigators judgment	
Comparison groups	4_rhNGF10_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.016
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	25.8
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	3.66
upper limit	47.87

Statistical analysis title	Complete Healing at Week 4_rhNGF20 vs veich
Statistical analysis description: according to investigator's judgment	
Comparison groups	5_rhNGF20_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.002
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	34.7

Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	11.91
upper limit	57.41

Secondary: Percentage of patients experiencing complete healing at week 8 by central reading and investigator

End point title	Percentage of patients experiencing complete healing at week 8 by central reading and investigator ^[4]
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End point description:

percentage of patients who achieved complete healing of the PED or corneal ulcer at 8 weeks as measured by central reading and investigator.

End point type	Secondary
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End point timeframe:

analysis conducted at 8 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is evaluated only for the selected group : all the available results have been reported.

End point values	4_rhNGF10_Phase 2_treatment	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	52	
Units: percentage				
central reading_yes	78	83	56	
central reading_no	22	17	44	
investigator_yes	79	79	53	
investigator_no	21	21	47	

Statistical analyses

Statistical analysis title	Complete Healing Week 8_rhNGF10vs veich_Central
Comparison groups	4_rhNGF10_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.031
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	21.9

Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	0.07
upper limit	43.64

Statistical analysis title	Complete Healing Week 8_rhNGF20vs veich_Central
Comparison groups	5_rhNGF20_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.008
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	26.9
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	5.57
upper limit	48.28

Statistical analysis title	Complete Healing Week 8_rhNGF10vs veich_Investigat
Statistical analysis description: according to investigator's judgment	
Comparison groups	4_rhNGF10_Phase 2_treatment v 6_vehicle group_Phase 2_treatment
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.011
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	26.1
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	4.18
upper limit	48.01

Statistical analysis title	Complete Healing Week 8_rhNGF20vs veich_Investigat
Statistical analysis description: according to investigator's judgment	
Comparison groups	5_rhNGF20_Phase 2_treatment v 6_vehicle group_Phase 2_treatment

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.014
Method	Chi-squared
Parameter estimate	difference in percentage
Point estimate	25.9
Confidence interval	
level	Other: 97.06 %
sides	2-sided
lower limit	3.55
upper limit	48.33

Secondary: Visual Analogue Scale (VAS) for ocular tolerability

End point title	Visual Analogue Scale (VAS) for ocular tolerability
End point description:	
<p>Ocular tolerability was recorded by the patient on a VAS scale from 0 to 100 mm, where a higher VAS score indicates worse ocular symptoms (0 means no symptoms and 100 means the worst possible discomfort). The overall VAS score for ocular tolerability was calculated as the mean of the individual VAS scores for the 7 different symptoms (foreign body sensation, burning/stinging, itching, ocular pain, sticky feeling, blurred vision and photophobia). A summary of ocular tolerability as measured by the VAS for the Safety population is provided. Overall ocular tolerability VAS scores decreased from Baseline to Week 8 in the rhNGF treatment groups and the vehicle control group, indicating an improvement in ocular tolerability.</p> <p>Result are below reported as per symptoms at week 8 (for treatment period) and week 20 (for Follow Up period). Results described in the CSR Addendum Report are attached.</p>	
End point type	Secondary
End point timeframe:	
period 1 (8 weeks) and 2 (Follow Up period of 12 weeks, untill week 20)	

End point values	1_rhNGF10_Phase 1_treatment	1_rhNGF10_Phase 1_FU	2_rhNGF20_Phase 1_treatment	2_rhNGF20_Phase 1_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: VAS Scale				
arithmetic mean (standard deviation)				
Foreign Body Sensation_Baseline	50.4 (± 25.68)	50.4 (± 25.68)	24 (± 19.76)	24 (± 19.76)
Foreign Body Sensation_CFB	-21.2 (± 25.96)	-20 (± 30.32)	-12.9 (± 17.03)	-13 (± 25.3)
burning/stinging_baseline	41.4 (± 30.85)	41.4 (± 30.85)	30.7 (± 38.78)	30.7 (± 38.78)
burning/stinging_CFB	-14.7 (± 38.02)	-18 (± 41.65)	-12.1 (± 28.27)	-16.5 (± 17.13)
itching_baseline	17 (± 27.4)	17 (± 27.4)	18.7 (± 19.62)	18.7 (± 19.62)
itching_CFB	-3 (± 17.93)	-7.8 (± 27.18)	-10 (± 23.1)	-4.2 (± 28.51)
ocular pain_baseline	34.1 (± 36.96)	34.1 (± 36.96)	33.6 (± 34.73)	33.6 (± 34.73)
ocular pain_CFB	-21.2 (± 28.96)	-16 (± 28.59)	-6 (± 30.72)	-9.3 (± 11.86)
sticky feeling_baseline	47.6 (± 34.14)	47.6 (± 34.14)	32.1 (± 35.34)	32.1 (± 35.34)

sticky feeling_CFB	-7.2 (± 42.82)	-19.8 (± 22.18)	-18.7 (± 38.32)	-0.7 (± 12.52)
blurred vision_baseline	71 (± 38.37)	71 (± 38.37)	85.7 (± 14.74)	85.7 (± 14.74)
blurred vision_CFB	-25.7 (± 34.37)	-26.5 (± 31.18)	-25 (± 32.15)	-26.2 (± 17.93)
photophobia_baseline	64.7 (± 42.9)	64.7 (± 42.9)	66.6 (± 29.85)	66.6 (± 29.85)
photophobia_CFB	-19.5 (± 27.98)	-20.3 (± 28.63)	-20.7 (± 34.13)	-26 (± 39.88)

End point values	3_vehicle group_Phase 1_treatment	3_vehicle group_Phase 1_FU	4_rhNGF10_Phase 2_treatment	4_rhNGF10_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	52	45
Units: VAS Scale				
arithmetic mean (standard deviation)				
Foreign Body Sensation_Baseline	20.5 (± 29.23)	20.5 (± 29.23)	34.8 (± 29.4)	34.8 (± 29.4)
Foreign Body Sensation_CFB	-16 (± 65.05)	-52 (± 0)	-8.8 (± 34.68)	-16.6 (± 31.26)
burning/stinging_baseline	18 (± 28.57)	18 (± 28.57)	32.5 (± 32.88)	32.5 (± 32.88)
burning/stinging_CFB	-28.5 (± 23.33)	-12 (± 0)	-3.8 (± 42.13)	-14.9 (± 40.35)
itching_baseline	7.8 (± 15.5)	7.8 (± 15.5)	24.1 (± 27.48)	24.1 (± 27.48)
itching_CFB	-15.5 (± 21.92)	-31 (± 0)	-10.8 (± 29.25)	-10.2 (± 30.62)
ocular pain_baseline	19 (± 38)	19 (± 38)	32.8 (± 34.86)	32.8 (± 34.86)
ocular pain_CFB	-23 (± 32.53)	-26 (± 0)	-2 (± 43)	-16.7 (± 34.66)
sticky feeling_baseline	15.5 (± 23.69)	15.5 (± 23.69)	26.6 (± 29.65)	26.6 (± 29.65)
sticky feeling_CFB	-11 (± 5.66)	-2 (± 0)	-11.7 (± 30.17)	-13.3 (± 30.75)
blurred vision_baseline	93.5 (± 7.9)	93.5 (± 7.9)	80.2 (± 25.18)	80.2 (± 25.18)
blurred vision_CFB	-22 (± 31.11)	-14 (± 0)	-24.9 (± 35.33)	-16.5 (± 38.43)
photophobia_baseline	30.3 (± 26.21)	30.3 (± 26.21)	64.3 (± 32.07)	64.3 (± 32.07)
photophobia_CFB	-30.5 (± 43.13)	-61 (± 0)	-17.8 (± 41.23)	-24.2 (± 37.51)

End point values	5_rhNGF20_Phase 2_treatment	5_rhNGF20_Phase 2_FU	6_vehicle group_Phase 2_treatment	6_vehicle group_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	39	52	48
Units: VAS Scale				
arithmetic mean (standard deviation)				
Foreign Body Sensation_Baseline	35.4 (± 34.79)	35.4 (± 34.79)	37.7 (± 36.49)	37.7 (± 36.49)
Foreign Body Sensation_CFB	-16.5 (± 36.87)	-22.4 (± 38.77)	-20.9 (± 35.86)	-20.7 (± 30.57)
burning/stinging_baseline	26.5 (± 30.86)	26.5 (± 30.86)	30.2 (± 32.21)	30.2 (± 32.21)
burning/stinging_CFB	-2.5 (± 26.76)	-10.8 (± 31.51)	-18 (± 32.97)	-14.7 (± 37.54)
itching_baseline	21.8 (± 28.68)	21.8 (± 28.68)	22.9 (± 28.43)	22.9 (± 28.43)

itching_CFB	-7.3 (± 22.67)	-11.9 (± 23.05)	-8.9 (± 25.59)	-4.8 (± 30.71)
ocular pain_baseline	21.1 (± 28.38)	21.1 (± 28.38)	28.8 (± 32.82)	28.8 (± 32.82)
ocular pain_CFB	2 (± 37.25)	-12.1 (± 31.25)	-16.3 (± 30.52)	-18.3 (± 34.3)
sticky feeling_baseline	17.4 (± 22.07)	17.4 (± 22.07)	26.1 (± 31.93)	26.1 (± 31.93)
sticky feeling_CFB	-4.3 (± 29.55)	-11.4 (± 31.11)	-10.7 (± 29.95)	-8.3 (± 30.62)
blurred vision_baseline	83.2 (± 24.45)	83.2 (± 24.45)	78.5 (± 24.68)	78.5 (± 24.68)
blurred vision_CFB	-26.2 (± 31.58)	-25.7 (± 34.41)	-17.4 (± 28.55)	-17.4 (± 27.14)
photophobia_baseline	57.6 (± 36.1)	57.6 (± 36.1)	65.2 (± 34.71)	65.2 (± 34.71)
photophobia_CFB	-13.2 (± 40.44)	-21 (± 38.76)	-17.5 (± 29.02)	-14.6 (± 29.19)

Attachments (see zip file)	14.3.6.2c VAS.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Best Corrected Distance Visual Acuity (BCDVA)

End point title	Best Corrected Distance Visual Acuity (BCDVA)
End point description:	
Best-Corrected Distance Visual Acuity (BCDVA) by means of the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart at 4 meters (13 feet). During the treatment period(phase1), an improvement was seen in the mean BCDVA scores in both rhNGF treatment groups, which was not observed in the vehicle group. During the follow-up period, a greater improvement in the mean BCDVA scores was observed in both rhNGF treatment groups (with a higher improvement in the rhNGF 20 µg/ml group). During the controlled treatment period(phase2), a greater improvement in the mean BCDVA score was observed in both rhNGF treatment groups compared to the vehicle group. During the uncontrolled treatment period(phase2) an increase was seen in the mean BCDVA score in the rhNGF 20 µg/ml group. During the follow-up period(phase2) an improvement in the mean BCDVA score was observed in both rhNGF treatment groups and the vehicle. Data reported refers to week n° 8 (treatment group) and n°12/20(FU group)	
End point type	Secondary
End point timeframe:	
period 1 (8 weeks) and 2 (Follow Up period of 12 weeks, until week 20). Results described in the CSR Addendum Report are attached.	

End point values	1_rhNGF10_Phase 1_treatment	1_rhNGF10_Phase 1_FU	2_rhNGF20_Phase 1_treatment	2_rhNGF20_Phase 1_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: Number of ETDRS letters				
arithmetic mean (standard deviation)				
baseline	42 (± 28.25)	42 (± 28.25)	30.4 (± 24.85)	30.4 (± 24.85)
change from baseline	9.3 (± 5.89)	11.2 (± 7.47)	8.7 (± 12.41)	7 (± 9.8)

End point values	3_vehicle group_Phase 1_treatment	3_vehicle group_Phase 1_FU	4_rhNGF10_Ph ase 2_treatment	4_rhNGF10_Ph ase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	52	45
Units: Number of ETDRS letters				
arithmetic mean (standard deviation)				
baseline	9.5 (± 11.96)	9.5 (± 11.96)	30.7 (± 28.35)	30.7 (± 28.35)
change from baseline	-1 (± 1.41)	-6 (± 0)	15.8 (± 16.82)	13.2 (± 16.8)

End point values	5_rhNGF20_Ph ase 2_treatment	5_rhNGF20_Ph ase 2_FU	6_vehicle group_Phase 2_treatment	6_vehicle group_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	39	52	48
Units: Number of ETDRS letters				
arithmetic mean (standard deviation)				
baseline	24.2 (± 25.88)	24.2 (± 25.88)	32.4 (± 26.07)	32.4 (± 26.07)
change from baseline	11.9 (± 20.9)	14.2 (± 19.06)	6.9 (± 15.44)	8.8 (± 14.27)

Attachments (see zip file)	14.3.9c BCDVA.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Intraocular Pressure (IOP)

End point title	Intraocular Pressure (IOP)
End point description:	
IOP was measured using a Goldmann applanation tonometer, a handheld applanation tonometer [eg, Tonopen], or other tonometer, after the instillation of a topical anesthetic. During the follow-up period (phase1), minimal fluctuations in IOP were observed in all 3 treatment groups. Minimal fluctuations in IOP were observed during the uncontrolled treatment period and during the follow-up period (phase2). There were no notable trends or differences between treatment groups. Results described in the CSR Addendum Report are attached.	
End point type	Secondary
End point timeframe:	
period 1 (8 weeks) and 2 (Follow Up period of 12 weeks, untill week 20)	

End point values	1_rhNGF10_Phase 1_treatment	1_rhNGF10_Phase 1_FU	2_rhNGF20_Phase 1_treatment	2_rhNGF20_Phase 1_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: mmHg				
arithmetic mean (standard deviation)				
baseline	16.1 (± 3.85)	16.1 (± 3.85)	11.3 (± 3.68)	11.3 (± 3.68)
change from baseline	-1.8 (± 2.48)	-2.2 (± 2.49)	1.9 (± 5.24)	2.3 (± 3.78)

End point values	3_vehicle group_Phase 1_treatment	3_vehicle group_Phase 1_FU	4_rhNGF10_Phase 2_treatment	4_rhNGF10_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	52	45
Units: mmHg				
arithmetic mean (standard deviation)				
baseline	11.8 (± 3.3)	11.8 (± 3.3)	14.3 (± 3.16)	14.3 (± 3.16)
change from baseline	3.5 (± 2.12)	-3 (± 0)	-0.1 (± 3.71)	0.2 (± 3.25)

End point values	5_rhNGF20_Phase 2_treatment	5_rhNGF20_Phase 2_FU	6_vehicle group_Phase 2_treatment	6_vehicle group_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	39	52	48
Units: mmHg				
arithmetic mean (standard deviation)				
baseline	14 (± 3.06)	14 (± 3.06)	14.1 (± 3.16)	14.1 (± 3.16)
change from baseline	0.9 (± 2.61)	0.1 (± 3.64)	0.8 (± 3.43)	0.6 (± 3.93)

Attachments (see zip file)	14.3.7.1c IOP.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Dilated fundus ophthalmoscopy

End point title	Dilated fundus ophthalmoscopy
End point description:	
Dilated fundus ophthalmoscopy was performed at specific time points to assess the retina, macula, choroid and optic nerve head after dilation of the pupil. Percentage of patients with each rating is summarized for each eye structure by treatment and visit for the controlled treatment period and follow-up period for Phase I and Phase II separately. Shifts from baseline (from normal to abnormal) results are reported for eye structure (Vitreous, Retina macula, Choroid, Optic nerve) at week 8 (for treatment group). Summary of fundus ophthalmoscopy by treatment and visit is reported in the table attached.	
End point type	Secondary

End point timeframe:

period 1 (8 weeks) and 2 (Follow Up period of 12 weeks, untill week 20)

End point values	1_rhNGF10_Phase 1_treatment	2_rhNGF20_Phase 1_treatment	3_vehicle group_Phase 1_treatment	4_rhNGF10_Phase 2_treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	4	52
Units: 0-100%				
Vitreous	0	0	25	2
Retina macula	0	0	0	0
Choroid	0	0	25	0
Optic nerve	0	0	0	0

End point values	5_rhNGF20_Phase 2_treatment	6_vehicle group_Phase 2_treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: 0-100%				
Vitreous	0	0		
Retina macula	2	0		
Choroid	0	0		
Optic nerve	0	0		

Attachments (see zip file)	14.3.8.1a Summary of Fundus Ophthalmoscopy_Phase 1/14. 14.3.8.1b Summary of Fundus Ophthalmoscopy_Phase2/14.
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Statistical analyses

No statistical analyses for this end point

Secondary: anti -NGF antibodies

End point title	anti -NGF antibodies ^[5]
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End point description:

Shifts from Baseline to post-Baseline visits for anti-NGF antibodies for the Safety population during the controlled treatment period (week 8 values) and follow-up period (20 weeks values) for phase 2 arms are hereto reported (as percentage from positive to positive).

End point type	Secondary
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End point timeframe:

period 2 (Follow Up period of 12 weeks, untill week 20)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is evaluated only for the selected group : all the available results have been reported.

End point values	4_rhNGF10_Phase 2_treatment	4_rhNGF10_Phase 2_FU	5_rhNGF20_Phase 2_treatment	5_rhNGF20_Phase 2_FU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	45	52	39
Units: percentage	0	0	0	0

End point values	6_vehicle group_Phase 2_treatment	6_vehicle group_Phase 2_FU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	48		
Units: percentage	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

treatment period (8 weeks) and follow up period (12 weeks) for Phase 1 and Phase 2 patients.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	1_rhNGF10_Phase 1
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Reporting group description:

cohort1: active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF).

Reporting group title	2_rhNGF20_Phase 1
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Reporting group description:

cohort 2: active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Reporting group title	3_vehicle group_Phase 1
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Reporting group description:

cohort 1 and 2: vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Reporting group title	4_rhNGF10_Phase 2
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Reporting group description:

active treatment with rhNGF 10 µg/ml. One drop six times a day (one 35 µl drop equals to 0.35 µg of rhNGF)

Reporting group title	5_rhNGF20_Phase 2
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Reporting group description:

active treatment with rhNGF 20 µg/ml. One drop 6 times a day (one 35 µl drop equals to 0.70 µg of rhNGF)

Reporting group title	6_vehicle group_Phase 2
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Reporting group description:

vehicle control arm. Ophthalmic solution of the same composition as the test product with the exception of rhNGF. One drop six times a day for the entire period

Serious adverse events	1_rhNGF10_Phase 1	2_rhNGF20_Phase 1	3_vehicle group_Phase 1
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	3 / 4 (75.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Reporting groups 4 and 5: severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Aortic dissection	Additional description: Reporting group 5: Severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic rupture	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic vascular disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Corneal graft rejection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: reporting groups 6 and 7 : Severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
Additional description: patient of reporting group 4 had a severe SAE			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
Additional description: reporting group 4: Severe SAE			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual acuity reduced	Additional description: visual acuity reduction of 13 letters		
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal endotheliitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal epithelium defect			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal neovascularisation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal opacity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neurotrophic keratopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder prolapse			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes ophthalmic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	4_rhNGF10_Phase 2	5_rhNGF20_Phase 2	6_vehicle group_Phase 2
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 52 (25.00%)	14 / 52 (26.92%)	4 / 52 (7.69%)
number of deaths (all causes)	5	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Reporting groups 4 and 5: severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Vascular disorders			
Aortic dissection	Additional description: Reporting group 5: Severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic rupture	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diabetic vascular disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	1 / 1	0 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Corneal graft rejection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: reporting groups 6 and 7 : Severe SAE		
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Dyspnoea	Additional description: reporting group 5: Severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction	Additional description: patient of reporting group 4 had a severe SAE		
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia	Additional description: reporting group 4: Severe SAE		
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Visual acuity reduced	Additional description: visual acuity reduction of 13 letters		
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal endotheliitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal epithelium defect			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal oedema			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye inflammation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal neovascularisation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal opacity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurotrophic keratopathy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder prolapse			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal abscess			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes ophthalmic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	1_rhNGF10_Phase 1	2_rhNGF20_Phase 1	3_vehicle group_Phase 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	5 / 7 (71.43%)	1 / 4 (25.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aortic rupture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diabetic vascular disorder			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diastolic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Shock haemorrhagic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Instillation site pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Instillation site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			

Corneal graft rejection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Immunodeficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Reproductive system and breast disorders Uterine prolapse subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory distress subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory failure subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 7 (28.57%) 2	0 / 4 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 4 (0.00%) 0
Investigations Haematocrit decreased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intraocular pressure increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vital dye staining cornea present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Periorbital haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Suture related complication			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Clavicle fracture			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Facial bones fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pelvic fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tibia fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Transplant failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Arrhythmia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
headache			

subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
eye pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 4 (25.00%)
occurrences (all)	0	6	2
eye inflammation			

subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Visual acuity reduced			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	4	1	1
Photophobia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Conjunctival hyperaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Corneal epithelium defect			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Corneal lesion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Erythema of eyelid			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
eye irritation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
eyelid margin crusting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Foreign body sensation in eyes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Iridocyclitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Photopsia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ulcerative keratitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
vitreous haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Corneal decompensation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Corneal oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ocular hyperemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
retinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blepharitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lacrimation decreased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal deposits			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye discharge			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abnormal sensation in eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Asthenopia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal endotheliitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal opacity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye allergy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eyelid pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eyelid ptosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lagophthalmos			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
macular fibrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ocular discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Posterior capsule opacification			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lenticular opacities			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Meibomianitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pseudopterygium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retinal cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal erosion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal neovascularisation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neurotrophic keratopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diverticular perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastric polyps			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
onychoclasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diabetic foot			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			

Renal colic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Bladder prolapse subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Muscle spasms subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 4 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Infections and infestations			
influenza subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 4 (0.00%) 0
Keratitis herpetic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 4 (25.00%) 1
Corneal infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 4 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Conjunctivitis bacterial subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Corneal abscess subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
Diverticulitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Helicobacter gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes ophthalmic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
blister infected			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Catheter site infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes simplex ophtalmic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes zoster ophtalmic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	0 / 4 (0.00%) 0
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Non-serious adverse events	4_rhNGF10_Phase 2	5_rhNGF20_Phase 2	6_vehicle group_Phase 2
Total subjects affected by non-serious adverse events subjects affected / exposed	23 / 52 (44.23%)	23 / 52 (44.23%)	21 / 52 (40.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Malignant neoplasm progression subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Vascular disorders Aortic dissection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Venous thrombosis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Aortic rupture subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Deep vein thrombosis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Diabetic vascular disorder subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Diastolic hypotension subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Shock haemorrhagic subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0

General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	4 / 52 (7.69%)	4 / 52 (7.69%)	6 / 52 (11.54%)
occurrences (all)	4	6	6
Fatigue			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Instillation site pruritus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Instillation site pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Impaired healing			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Corneal graft rejection			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	1 / 52 (1.92%)
occurrences (all)	1	4	1
Immunodeficiency			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0

Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Respiratory distress			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Investigations			
Haematocrit decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Intraocular pressure increased			
subjects affected / exposed	2 / 52 (3.85%)	4 / 52 (7.69%)	0 / 52 (0.00%)
occurrences (all)	2	4	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0

Blood creatine increased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Heart rate increased subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Vital dye staining cornea present subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Periorbital haematoma subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Suture related complication subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 2
Clavicle fracture subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Facial bones fracture subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Femur fracture subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Pelvic fracture subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Tibia fracture			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Transplant failure			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Arrhythmia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Myocardial infarction			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
headache			
subjects affected / exposed	2 / 52 (3.85%)	4 / 52 (7.69%)	2 / 52 (3.85%)
occurrences (all)	2	4	2
Hypoaesthesia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Trigeminal neuralgia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Burning sensation			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 3	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Ear pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Eye disorders eye pain subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	7 / 52 (13.46%) 7	5 / 52 (9.62%) 7
eye inflammation subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	5 / 52 (9.62%) 5	2 / 52 (3.85%) 2
Photophobia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	1 / 52 (1.92%) 1	1 / 52 (1.92%) 1
Corneal epithelium defect			

subjects affected / exposed	1 / 52 (1.92%)	5 / 52 (9.62%)	1 / 52 (1.92%)
occurrences (all)	1	5	2
Corneal lesion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	3 / 52 (5.77%)
occurrences (all)	2	1	3
Erythema of eyelid			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
eye irritation			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
eyelid margin crusting			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Foreign body sensation in eyes			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	1	0	1
Iridocyclitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Ulcerative keratitis			
subjects affected / exposed	4 / 52 (7.69%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	4	1	0
Vision blurred			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	2 / 52 (3.85%)
occurrences (all)	2	0	2
vitreous haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
Corneal decompensation			

subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Corneal oedema			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Keratitis			
subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	0 / 52 (0.00%)
occurrences (all)	0	6	0
ocular hyperemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	2 / 52 (3.85%)
occurrences (all)	0	1	2
retinal haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	3 / 52 (5.77%)	6 / 52 (11.54%)	1 / 52 (1.92%)
occurrences (all)	3	6	2
Eye pruritus			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Lacrimation increased			
subjects affected / exposed	3 / 52 (5.77%)	0 / 52 (0.00%)	2 / 52 (3.85%)
occurrences (all)	3	0	2
Lacrimation decreased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Corneal deposits			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 52 (0.00%)
occurrences (all)	0	3	0
Eye discharge			
subjects affected / exposed	1 / 52 (1.92%)	2 / 52 (3.85%)	0 / 52 (0.00%)
occurrences (all)	1	2	0
Abnormal sensation in eye			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Asthenopia			

subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	2	0	2
Corneal endotheliitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Corneal opacity			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Eye allergy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	1 / 52 (1.92%)
occurrences (all)	0	2	1
Eyelid pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	2	0	1
Eyelid ptosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Lagophthalmos			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
macular fibrosis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Ocular discomfort			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	2 / 52 (3.85%)
occurrences (all)	0	0	2
Posterior capsule opacification			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
Lenticular opacities			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Meibomianitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Pseudopterygium			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Retinal cyst			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	3 / 52 (5.77%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	3	0	0
Corneal erosion			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	5	1	0
Corneal neovascularisation			
subjects affected / exposed	2 / 52 (3.85%)	2 / 52 (3.85%)	1 / 52 (1.92%)
occurrences (all)	2	4	1
Neurotrophic keratopathy			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	3	1	0
Conjunctivitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
toothache			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0

Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Diverticular perforation subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Gastric polyps subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Skin and subcutaneous tissue disorders dry skin subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
onychoclasia subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Diabetic foot subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	2 / 52 (3.85%) 2	0 / 52 (0.00%) 0
Bladder prolapse subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Intervertebral disc protrusion			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Infections and infestations			
influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Keratitis herpetic			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 52 (0.00%)
occurrences (all)	0	2	0
Corneal infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 52 (7.69%)	3 / 52 (5.77%)	2 / 52 (3.85%)
occurrences (all)	4	4	2
Gastroenteritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	1	0	1
Conjunctivitis bacterial			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Corneal abscess			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Diverticulitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
oral herpes			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Staphylococcal infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 2	0 / 52 (0.00%) 0
Helicobacter gastritis subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Herpes ophthalmic subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
blister infected subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Catheter site infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Cystitis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 2	0 / 52 (0.00%) 0
Herpes simplex ophtalmic subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1
Herpes zoster ophtalmic subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Onychomycosis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0
Tonsillitis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	0 / 52 (0.00%) 0

Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Vitamin B12 deficiency			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 52 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	<p>Protocol Amendment #1: the main changes to the protocol are listed below</p> <ul style="list-style-type: none">• Change in the study title• Change in the study population• Deletion of inclusion criteria #7• Addition of exclusion criteria #1• Specify that additional safety information continued to be collected within 4 weeks after the end of treatment• Further clarify the study design shown in Figures 1 and 2• Clarify the definition of deterioration and modify a secondary efficacy variable• Add an exploratory efficacy variable• Add that the grade of corneal fluorescein staining using the modified Oxford scale should be assessed at all visits where corneal fluorescein staining is performed• Add the laboratory that was in charge of the processing, storage and shipment of immunogenicity evaluation samples and the reading center in charge of the collection, classification and evaluation of the corneal photos
02 December 2013	<p>Amendment #2: main changes to the study protocol are listed below:</p> <ul style="list-style-type: none">• Permit a single additional course of treatment with rhNGF to patients experiencing a recurrent PED or corneal ulcer immediately after 8 weeks of treatment with study medications• Enlarge the visual acuity entry criteria• Permit treatment with preservative free antiviral eye drops to patients during the 8-week controlled treatment period that were considered to be at imminent risk of deterioration of their Stage 2 or 3 NK in the opinion of the Investigator• Reflect sponsor organizational changes in regards to the pharmacovigilance main contact and in regards to the laboratory that was in charge of the PK analysis
31 March 2014	<p>Amendment #3: main changes are listed below.</p> <ul style="list-style-type: none">• Change in the assessment of the primary variable from the evaluation of the PED or corneal ulcer lesion done by the Investigator to the evaluation done by the central reading center. Consequently to this major change, the evaluation of the PED or corneal ulcer done by the Investigator at Week 4 was moved into the secondary variables and the assessment of complete healing of the PED or corneal ulcer determined by the reading center at Weeks 6 and 8 was moved from exploratory variables to secondary variables.• Changed the primary endpoint to be the last observation carried forward (LOCF), where it had previously used no imputation• The secondary efficacy endpoints related to the controlled treatment period concerning the percentage of patients experiencing complete corneal clearing at Weeks 4, 6 and 8 were moved from the exploratory efficacy variables to the secondary efficacy variables.• Added clarification about data to be reported in the main CSR and an addendum to the CSR. The database was locked and the study was completed after the last patient had completed 12 weeks of the follow-up period. However, after the database lock, patients continued with scheduled visits for the remainder of the 48- or 56-week follow-up period and the long term safety/efficacy data collected during these followup visits will be described in an addendum to the final main CSR.• Added clarification that the results for patients enrolled during the Phase I segment of the study were analyzed separately from the results for patients enrolled during the Phase II segment of the study• Added further specification about the handling of missing data• Added text for sponsor organizational changes: Change of the name of the Sponsor from Dompé s.p.a. to Dompé farmaceutici s.p.a.; Change of the pharmacovigilance main contact; Change of the medical expert; inclusion of a clinical development specialist; Administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported