



## Clinical trial results:

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

## Summary

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

## Results information

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

## Trial information

### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | NGF0116 |
|-----------------------|---------|

### Additional study identifiers

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

Notes:

## Sponsors

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

Notes:

## Paediatric regulatory details

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

Notes:

## Results analysis stage

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

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 12 January 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 180 |
| Worldwide total number of subjects   | 180        |
| EEA total number of subjects         | 180        |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 173 |
| From 65 to 84 years                       | 7   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 180 patients were screened and all of them were randomized to the assigned treatment: 120 patients were randomised to receive rhNGF and 60 were randomised to receive vehicle.

A total of 160 patients (88.9% of screened patients), 105 (87.5%) in the rhNGF group and 55 (91.7%) in the vehicle group, completed the study.

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

It is a double-masked study

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | rhNGF |

Arm description:

rhNGF 20 µg/mL.

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

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

Dosage and administration details:

Recombinant human Nerve Growth Factor (rhNGF) 20 µg/mL vials.

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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Vehicle |
|------------------|---------|

Arm description:

Vehicle.

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

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

Dosage and administration details:

Vehicle vials.

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

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

## Period 2

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

Blinding implementation details:

It is a double-masked study

## Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | rhNGF |

Arm description:

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

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |
| <b>Arm title</b>  | Vehicle         |

Arm description:

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

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

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

## Baseline characteristics

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | rhNGF |
|-----------------------|-------|

Reporting group description:

rhNGF 20 µg/mL.

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

|                       |         |
|-----------------------|---------|
| Reporting group title | Vehicle |
|-----------------------|---------|

Reporting group description:

Vehicle.

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

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

### Subject analysis sets

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | rhNGF - SAF |
|----------------------------|-------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

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

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Vehicle - SAF |
|----------------------------|---------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | rhNGF - FAS |
|----------------------------|-------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

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

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Vehicle - FAS |
|----------------------------|---------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

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

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

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

## End points

### End points reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | rhNGF |
|-----------------------|-------|

Reporting group description:

rhNGF 20 µg/mL.

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

|                       |         |
|-----------------------|---------|
| Reporting group title | Vehicle |
|-----------------------|---------|

Reporting group description:

Vehicle.

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

|                       |       |
|-----------------------|-------|
| Reporting group title | rhNGF |
|-----------------------|-------|

Reporting group description:

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

|                       |         |
|-----------------------|---------|
| Reporting group title | Vehicle |
|-----------------------|---------|

Reporting group description:

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

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | rhNGF - SAF |
|----------------------------|-------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

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

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Vehicle - SAF |
|----------------------------|---------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | rhNGF - FAS |
|----------------------------|-------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

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

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Vehicle - FAS |
|----------------------------|---------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

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

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

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in SANDE Scores for Frequency and Severity Assessed at 8 Weeks of Treatment. |
|-----------------|---|

End point description:

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

If at least one SANDE assessment was missing at Week 8, the values of the last post-baseline assessment (including those from unscheduled visits) with non-missing values for frequency and severity were imputed (last observation carried forward, LOCF).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|



End point timeframe:

Week 8

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

### Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 8

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

### Statistical analyses

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

Notes:

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

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

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

End point description:

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

Data for the main eye are reported.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to weeks 4, 8 and 12

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

Notes:

[4] - Week 4 = 110

Week 8 = 107

Week 12 = 107

[5] - Week 4 = 58

Week 8 = 58

Week 12 = 55

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

Data for the main eye are reported.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to weeks 4, 8 and 12

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

Notes:

[6] - Week 4 = 110

Week 8 = 107

Week 12 = 107

[7] - Week 4 = 58

Week 8 = 58

Week 12 = 55

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes in Cochet-Bonnet corneal aesthesiometry

|                 |   |
|-----------------|---|
| End point title | Changes in Cochet-Bonnet corneal aesthesiometry |
|-----------------|---|

End point description:

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

Data for the main eye are reported.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to week 8

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

Notes:

[8] - Superior nasal = 107

Inferior nasal = 107

Superior temporal = 107

Inferior temporal = 107

[9] - Superior nasal = 58

Inferior nasal = 58

Superior temporal = 58

Inferior temporal = 58

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to weeks 4, 8 and 12

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

Notes:

[10] - Frequency wk 4 = 110

Fr wk 8 & 12 = 107

Severity wk 4 = 110

Sev wk 8 & 12 = 107

[11] - Frequency Wk 4 & 8 = 58

Fr Wk 12 = 55

Severity Wk 4 & 8 = 58

Sev Wk 12 = 55

## Statistical analyses

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | rhNGF vs Vehicle |
|----------------------------|------------------|

Statistical analysis description:

Frequency - week 4

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | rhNGF - FAS v Vehicle - FAS |
|-------------------|-----------------------------|

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | rhNGF vs Vehicle            |
| Statistical analysis description: |                             |
| Severity - week 12                |                             |
| Comparison groups                 | rhNGF - FAS v Vehicle - FAS |

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

Notes:

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

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At weeks 4, 12

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

Notes:

[18] - n=110 at week 4

n=107 at week 12

[19] - n=55 at week 12

### Statistical analyses

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



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

Notes:

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

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

Notes:

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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At day 0 (baseline), at weeks 4, 8, and 12 (follow-up visit)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | rhNGF - SAF |
|-----------------------|-------------|

Reporting group description:

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

|                       |               |
|-----------------------|---------------|
| Reporting group title | Vehicle - SAF |
|-----------------------|---------------|

Reporting group description:

Safety set (SAF): the Safety Set was defined as all enrolled patients who received at least one dose of the IMP (vehicle) at the study eye(s).

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

Frequency threshold for reporting non-serious adverse events: 0.9 %

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 03 November 2016 | <ul style="list-style-type: none"><li>• The use of SANDE scoring system was updated and clarified</li><li>• The exclusion criterion No. 2 was modified with the specification that particular attention was to be paid to malignancies and neuro-oncological diseases</li><li>• A pregnancy test was added at Week 4 as per Clinical Trial Facilitation Group (CTFG) guideline</li><li>• The definition of accepted/forbidden medications was updated</li><li>• Criteria for study discontinuation were modified with the addition of safety concerns related to IMP</li><li>• The list of conditions which should not have to be considered, SAEs was modified</li><li>• Other minor changes or typographical errors correction were performed</li></ul> |
| 12 April 2017    | The secondary efficacy endpoint "Changes in Cornea vital staining with fluorescein (NEI scales)" was removed and was modified into a Co-Primary Efficacy Endpoint.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

There are no limitations or caveats to this summary of results

Notes: