



## Clinical trial results:

### A Multicenter, Randomized, Double-Masked, Placebo-Controlled Phase II Study to evaluate the Safety and Efficacy of Pro-ocular™ 0.5% and 1% in Patients with Dry Eye Syndrome

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2019-000747-27  |
| Trial protocol           | IT              |
| Global end of trial date | 26 October 2022 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 07 January 2026 |
| First version publication date | 07 January 2026 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 049/SI |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04645446 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                        |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | SIFI S.p.A.                                                                                            |
| Sponsor organisation address | Via Ercole Patti 36, Aci Sant'Antonio, Catania, Italy,                                                 |
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Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 29 March 2023   |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 26 October 2022 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 26 October 2022 |
| 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 evaluate the efficacy of progesterone topical gel (0.5% and 1%) compared to placebo gel, when administered twice a day for 3 months (12 weeks) in patients with moderate to severe dry eye syndrome.

Protection of trial subjects:

This trial was conducted in accordance with the Declaration of Helsinki, ICH-GCP E6(R2), and applicable national regulations. Ethical approval was obtained from all relevant Italian Ethics Committees prior to study initiation. All participants provided written informed consent before undergoing any study-related procedures. For patients unable to read, an impartial witness was present during the consent process. The study design included strict inclusion and exclusion criteria to ensure participant safety and scientific integrity.

Adverse events (AEs) were systematically recorded and evaluated.

Blinding and randomization were centrally managed to protect against bias, and data confidentiality was maintained throughout.

Essential documents were archived per GCP standards. The study was monitored and audited by an independent CRO to ensure compliance and data integrity.

Background therapy:

Not applicable

Evidence for comparator:

Placebo was used as a comparator. The study design, being a multicenter, randomised, double-masked, placebo-controlled, Phase II superiority study is considered as the most suitable design to evaluate the potential efficacy and safety of Pro-ocular™ topical gel.

The placebo control allowed for unbiased assessment of treatment effects in the absence of a universally accepted standard therapy for dry eye syndrome.

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 18 February 2021 |
| 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: 91 |
| Worldwide total number of subjects   | 91        |
| EEA total number of subjects         | 91        |

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)                      | 50 |
| From 65 to 84 years                       | 41 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Start of Recruitment (FPFV): 18 February 2021 - End of Trial (LPLV): 26 October 2022 - Trial Completion (Last Site Close-Out Visit): 27 April 2023

Study conducted in 4 sites in Italy: Ospedale Luigi Sacco, MI, AOU Careggi, FI, Policlinico G. Martino, ME, Ospedale San Marco, CT.

### Pre-assignment

Screening details:

101 subjects pre-screened: 5 withdrawal prior enrolment; 96 enrolled; 5 failure; 91 randomized. Screening included 15-day wash-out for anti-inflammatory topical treatments and 7-day for contact lenses. Exclusions due to withdrawal, lost to follow-up, or protocol criteria. Inclusion: age  $\geq 18$ , dry eye  $\geq 3$  months, NEI  $> 3$ , TBUT  $\leq 5$ s, Schirmer's 1-10

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 96 <sup>[1]</sup> |
| Number of subjects completed | 91                |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 3 |
| Reason: Number of subjects | Lost to Follow Up: 1            |
| Reason: Number of subjects | Physician Decision: 1           |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In enrolled patient count, 5 withdrawal prior enrolment were not included.

Please also refer to screening details field in pre-assignment period.

### Period 1

|                              |                                              |
|------------------------------|----------------------------------------------|
| Period 1 title               | Interventional Phase (overall 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:

Blinding was maintained by centralized randomization via IWRS. Identical appearance, packaging, and administration of active and placebo gels.

Placebo contained titanium dioxide instead of progesterone, but was otherwise indistinguishable.

Emergency unblinding was allowed via IWRS only in medical emergencies.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| Arm title                    | Pro-ocular™ 0.5% |

Arm description:

Pro-ocular™ 0.5% topical gel (0.35 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Pro-ocular™  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Gel          |
| Routes of administration               | Ocular use   |

Dosage and administration details:

0.35 mg progesterone/dose, BID to forehead for 12 weeks

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Pro-ocular™ 1% |
|------------------|----------------|

Arm description:

Pro-ocular™ 1% topical gel (0.7 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Pro-ocular™  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Gel          |
| Routes of administration               | Ocular use   |

Dosage and administration details:

0.7 mg progesterone/dose, BID to forehead for 12 weeks

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

Arm description:

Placebo topical gel (no active ingredient; titanium dioxide instead of progesterone), identical in appearance and dosing to active gel (0.07g BID to forehead for 12 weeks).

|                                        |            |
|----------------------------------------|------------|
| Arm type                               | Placebo    |
| Investigational medicinal product name | Placebo    |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Gel        |
| Routes of administration               | Ocular use |

Dosage and administration details:

0.07g BID to forehead for 12 weeks

| <b>Number of subjects in period 1</b> | Pro-ocular™ 0.5% | Pro-ocular™ 1% | Placebo |
|---------------------------------------|------------------|----------------|---------|
| Started                               | 31               | 30             | 30      |
| Completed                             | 24               | 27             | 26      |
| Not completed                         | 7                | 3              | 4       |
| Consent withdrawn by subject          | 4                | 1              | -       |
| Physician decision                    | 1                | -              | -       |
| Adverse event, non-fatal              | -                | -              | 1       |
| Other                                 | -                | -              | 1       |
| Lost to follow-up                     | 2                | 1              | 2       |
| Protocol deviation                    | -                | 1              | -       |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Pro-ocular™ 0.5% |
|-----------------------|------------------|

Reporting group description:

Pro-ocular™ 0.5% topical gel (0.35 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Pro-ocular™ 1% |
|-----------------------|----------------|

Reporting group description:

Pro-ocular™ 1% topical gel (0.7 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo topical gel (no active ingredient; titanium dioxide instead of progesterone), identical in appearance and dosing to active gel (0.07g BID to forehead for 12 weeks).

| Reporting group values                             | Pro-ocular™ 0.5% | Pro-ocular™ 1% | Placebo |
|----------------------------------------------------|------------------|----------------|---------|
| Number of subjects                                 | 31               | 30             | 30      |
| Age categorical                                    |                  |                |         |
| Units: Subjects                                    |                  |                |         |
| In utero                                           |                  |                |         |
| Preterm newborn infants (gestational age < 37 wks) |                  |                |         |
| Newborns (0-27 days)                               |                  |                |         |
| Infants and toddlers (28 days-23 months)           |                  |                |         |
| Children (2-11 years)                              |                  |                |         |
| Adolescents (12-17 years)                          |                  |                |         |
| Adults (18-64 years)                               |                  |                |         |
| From 65-84 years                                   |                  |                |         |
| 85 years and over                                  |                  |                |         |
| Age continuous                                     |                  |                |         |
| Units: years                                       |                  |                |         |
| arithmetic mean                                    | 62.4             | 61.7           | 59      |
| standard deviation                                 | ± 13.85          | ± 10.89        | ± 9.49  |
| Gender categorical                                 |                  |                |         |
| Units: Subjects                                    |                  |                |         |
| Female                                             | 28               | 27             | 27      |
| Male                                               | 3                | 3              | 3       |
| Race                                               |                  |                |         |
| Units: Subjects                                    |                  |                |         |
| American Indian / Alaska Native                    | 1                | 0              | 0       |
| Asian                                              | 0                | 0              | 1       |
| Native Hawaiian or Other Pacific Islander          | 0                | 0              | 0       |
| Black or African American                          | 0                | 0              | 0       |
| White / Caucasian                                  | 29               | 30             | 29      |
| Unknown or Not Reported                            | 0                | 0              | 0       |
| Other                                              | 1                | 0              | 0       |
| Smoking Status                                     |                  |                |         |

|                                                            |         |         |        |
|------------------------------------------------------------|---------|---------|--------|
| Units: Subjects                                            |         |         |        |
| Ex-Smoker                                                  | 3       | 3       | 3      |
| Current smoke                                              | 2       | 0       | 2      |
| Non-smoker                                                 | 26      | 27      | 25     |
| Alcohol consumption status                                 |         |         |        |
| Units: Subjects                                            |         |         |        |
| Yes                                                        | 0       | 0       | 1      |
| No                                                         | 31      | 30      | 29     |
| Use of Chlorinated Swimming Pool<br>More Than Twice A Week |         |         |        |
| Units: Subjects                                            |         |         |        |
| Yes                                                        | 0       | 0       | 0      |
| No                                                         | 31      | 30      | 30     |
| Use of Sunscreen on The Forehead or<br>Eye Area            |         |         |        |
| Units: Subjects                                            |         |         |        |
| Yes                                                        | 0       | 0       | 0      |
| No                                                         | 31      | 30      | 30     |
| Use of Contact Lenses                                      |         |         |        |
| Units: Subjects                                            |         |         |        |
| Yes                                                        | 1       | 0       | 0      |
| No                                                         | 30      | 30      | 30     |
| Duration of Smoking                                        |         |         |        |
| Units: Years                                               |         |         |        |
| arithmetic mean                                            | 21.3    | 33      | 34     |
| standard deviation                                         | ± 12.74 | ± 20.22 | ± 5.57 |

|                                                       |       |  |  |
|-------------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                         | Total |  |  |
| Number of subjects                                    | 91    |  |  |
| Age categorical                                       |       |  |  |
| Units: Subjects                                       |       |  |  |
| In utero                                              | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 0     |  |  |
| From 65-84 years                                      | 0     |  |  |
| 85 years and over                                     | 0     |  |  |
| Age continuous                                        |       |  |  |
| Units: years                                          |       |  |  |
| arithmetic mean                                       |       |  |  |
| standard deviation                                    | -     |  |  |
| Gender categorical                                    |       |  |  |
| Units: Subjects                                       |       |  |  |
| Female                                                | 82    |  |  |
| Male                                                  | 9     |  |  |

|                                                         |    |  |  |
|---------------------------------------------------------|----|--|--|
| Race                                                    |    |  |  |
| Units: Subjects                                         |    |  |  |
| American Indian / Alaska Native                         | 1  |  |  |
| Asian                                                   | 1  |  |  |
| Native Hawaiian or Other Pacific Islander               | 0  |  |  |
| Black or African American                               | 0  |  |  |
| White / Caucasian                                       | 88 |  |  |
| Unknown or Not Reported                                 | 0  |  |  |
| Other                                                   | 1  |  |  |
| Smoking Status                                          |    |  |  |
| Units: Subjects                                         |    |  |  |
| Ex-Smoker                                               | 9  |  |  |
| Current smoke                                           | 4  |  |  |
| Non-smoker                                              | 78 |  |  |
| Alcohol consumption status                              |    |  |  |
| Units: Subjects                                         |    |  |  |
| Yes                                                     | 1  |  |  |
| No                                                      | 90 |  |  |
| Use of Chlorinated Swimming Pool More Than Twice A Week |    |  |  |
| Units: Subjects                                         |    |  |  |
| Yes                                                     | 0  |  |  |
| No                                                      | 91 |  |  |
| Use of Sunscreen on The Forehead or Eye Area            |    |  |  |
| Units: Subjects                                         |    |  |  |
| Yes                                                     | 0  |  |  |
| No                                                      | 91 |  |  |
| Use of Contact Lenses                                   |    |  |  |
| Units: Subjects                                         |    |  |  |
| Yes                                                     | 1  |  |  |
| No                                                      | 90 |  |  |
| Duration of Smoking                                     |    |  |  |
| Units: Years                                            |    |  |  |
| arithmetic mean                                         |    |  |  |
| standard deviation                                      | -  |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                              |                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                        | Pro-ocular™ 0.5% |
| Reporting group description:<br>Pro-ocular™ 0.5% topical gel (0.35 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.                                 |                  |
| Reporting group title                                                                                                                                                                                        | Pro-ocular™ 1%   |
| Reporting group description:<br>Pro-ocular™ 1% topical gel (0.7 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.                                    |                  |
| Reporting group title                                                                                                                                                                                        | Placebo          |
| Reporting group description:<br>Placebo topical gel (no active ingredient; titanium dioxide instead of progesterone), identical in appearance and dosing to active gel (0.07g BID to forehead for 12 weeks). |                  |

### Primary: Mean change from Baseline (Visit 1 pre-dose) in Corneal Fluorescein Staining assessed by NEI scale at Week 12 (Day 84) (with Last Observation Carried Forward [LOCF] imputation)

|                                                  |                                                                                                                                                                                  |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                  | Mean change from Baseline (Visit 1 pre-dose) in Corneal Fluorescein Staining assessed by NEI scale at Week 12 (Day 84) (with Last Observation Carried Forward [LOCF] imputation) |
| End point description:<br>Data from Table 15 CSR |                                                                                                                                                                                  |
| End point type                                   | Primary                                                                                                                                                                          |
| End point timeframe:<br>Week 12                  |                                                                                                                                                                                  |

| End point values                     | Pro-ocular™ 0.5% | Pro-ocular™ 1%  | Placebo         |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 29               | 30              | 30              |  |
| Units: NEI scale points              |                  |                 |                 |  |
| arithmetic mean (standard deviation) |                  |                 |                 |  |
| Baseline                             | 7.4 (± 3)        | 7.7 (± 2.88)    | 8.2 (± 3.47)    |  |
| Week 12                              | 4.5 (± 2.92)     | 5.7 (± 3.85)    | 4.4 (± 3.20)    |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 15. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                   |                                             |
|-----------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b> | Statistical analysis primary endpoint n. 1  |
| Comparison groups                 | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo |

|                                         |                      |
|-----------------------------------------|----------------------|
| Number of subjects included in analysis | 89                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | < 0.1 <sup>[1]</sup> |
| Method                                  | ANCOVA               |

Notes:

[1] - Correzione per molteplicità: Holm-Bonferroni

**Primary: Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of Dryness/Irritation Patient Feeling assessed by Symptom Assessment in Dry Eye (SANDE) Questionnaire at Week 12 (Day 84) (with LOCF imputation).**

|                 |                                                                                                                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of Dryness/Irritation Patient Feeling assessed by Symptom Assessment in Dry Eye (SANDE) Questionnaire at Week 12 (Day 84) (with LOCF imputation). |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 15 CSR

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

End point timeframe:

Week 12

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: SANDE scale points            |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 70.2 (± 26.01)      | 63.9 (± 29.25)    | 74.7 (± 22.97)  |  |
| Week 12                              | 48.4 (± 28.23)      | 44.1 (± 32.25)    | 45.1 (± 25.62)  |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in su/Table 15. |
|-----------------------------------|--------------------------------------------------------------|

**Statistical analyses**

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis primary endpoint n. 2  |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo |
| Number of subjects included in analysis | 89                                          |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | < 0.1 <sup>[2]</sup>                        |
| Method                                  | ANCOVA                                      |

Notes:

[2] - Correzione per molteplicità: Holm-Bonferroni

**Secondary: Mean change from Baseline (Visit 1 pre-dose) in Corneal Fluorescein Staining assessed by NEI scale at Week 12 (Day 84).**

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Corneal |
|-----------------|---------------------------------------------------------|

End point description:

Data from Table 18 CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:

Pro-ocular 0.5%: 29

Pro-ocular 1%: 30

Placebo: 30

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 24                  | 28                | 27              |  |
| Units: NEI scale points              |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 7.4 (± 3.00)        | 7.7 (± 2.88)      | 8.2 (± 3.47)    |  |
| Week 12                              | 4.2 (± 2.63)        | 5.9 (± 3.83)      | 4.4 (± 3.23)    |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 18. |
|-----------------------------------|--------------------------------------------------------------|

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 1 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 79                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

## Secondary: Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of dryness/irritation patient feeling assessed by SANDE questionnaire at Week 12 (Day 84).

|                 |                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of dryness/irritation patient feeling assessed by SANDE questionnaire at Week 12 (Day 84). |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 20 (Global Score) CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:  
Pro-ocular 0.5%: 29  
Pro-ocular 1%: 30  
Placebo: 30

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 25                  | 28                | 27              |  |
| Units: SANDE scale points            |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 70.2 (± 26.01)      | 63.9 (± 29.25)    | 74.7 (± 22.97)  |  |
| Week 12                              | 46.6 (± 28.22)      | 42.8 (± 31.54)    | 44.0 (± 26.14)  |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in su/Table 20. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 2 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 80                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 12 (Day 84) (with LOCF imputation).

|                 |                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 12 (Day 84) (with LOCF imputation). |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 24 of CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:  
Pro-ocular 0.5%: 29  
Pro-ocular 1%: 30  
Placebo: 30

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

End point timeframe:

Week 12

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: NEI scale score               |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Nasal Total Baseline                 | 3.7 (± 2.89)        | 4.2 (± 2.70)      | 5.0 (± 3.27)    |  |
| Nasal Total Week 12                  | 2.0 (± 2.35)        | 3.3 (± 2.74)      | 3.5 (± 3.33)    |  |
| Temporal Total Baseline              | 3.3 (± 3.15)        | 3.8 (± 2.62)      | 4.5 (± 3.22)    |  |
| Temporal Total Week 12               | 1.8 (± 2.38)        | 2.7 (± 2.71)      | 3.6 (± 3.31)    |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 24. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 3 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 89                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 12 (Day 84).

|                            |                                                                                                                              |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title            | Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 12 (Day 84). |
| End point description:     |                                                                                                                              |
| Data from Table 24 of CSR. |                                                                                                                              |
| End point type             | Secondary                                                                                                                    |
| End point timeframe:       |                                                                                                                              |
| Week 12                    |                                                                                                                              |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 24                  | 28                | 27              |  |
| Units: NEI scale score               |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Nasal Total Baseline                 | 3.7 (± 2.89)        | 4.2 (± 2.70)      | 5.0 (± 3.27)    |  |
| Nasal Total Week 12                  | 1.7 (± 1.93)        | 3.4 (± 2.77)      | 3.5 (± 3.46)    |  |
| Temporal Total Baseline              | 3.3 (± 3.15)        | 3.8 (± 2.62)      | 4.5 (± 3.22)    |  |
| Temporal Total Week 12               | 1.5 (± 1.84)        | 2.9 (± 2.73)      | 3.6 (± 3.35)    |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 24. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 4 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 79                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Corneal Fluorescein Staining assessed by NEI scale at Week 2, 4, 8 (Day 14, 28, 56) as Intermediate Study Visits

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Corneal Fluorescein Staining assessed by NEI scale at Week 2, 4, 8 (Day 14, 28, 56) as Intermediate Study Visits |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.1 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

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

End point timeframe:

Week 2, 4, 8

| <b>End point values</b>              | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: NEI scale score               |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 7.4 (± 3)           | 7.7 (± 2.88)      | 8.2 (± 3.47)    |  |
| Week 2                               | 4.8 (± 3.51)        | 5.5 (± 3.88)      | 5.8 (± 2.98)    |  |
| Week 4                               | 4.2 (± 2.02)        | 5.9 (± 3.19)      | 5.1 (± 3.10)    |  |
| Week 8                               | 4.0 (± 2.82)        | 4.8 (± 3.08)      | 4.9 (± 3.98)    |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 5 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 89                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### **Secondary: Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of Dryness/Irritation Patient Feeling assessed by SANDE questionnaire at Week 2, 4, 8, 16 (Day 14, 28, 56,114) as Intermediate Study Visits.**

|                 |                                                                                                                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in sum of Frequency and Intensity of Dryness/Irritation Patient Feeling assessed by SANDE questionnaire at Week 2, 4, 8, 16 (Day 14, 28, 56,114) as Intermediate Study Visits. |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.25 (Global Score) Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

Subjects analysed at 16 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 27

Placebo: 25

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8, 16     |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: SANDE scale points            |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 70.2 (± 26.01)      | 63.9 (± 29.25)    | 74.7 (± 22.97)  |  |
| Week 2                               | 60.5 (± 25.59)      | 58.9 (± 31.14)    | 58.7 (± 26.94)  |  |
| Week 4                               | 56.0 (± 24.61)      | 52.3 (± 30.78)    | 52.2 (± 26.78)  |  |
| Week 8                               | 49.1 (± 23.55)      | 56.0 (± 28.62)    | 48.0 (± 25.45)  |  |
| Week 16                              | 43.8 (± 26.30)      | 43.1 (± 29.42)    | 36.7 (± 22.99)  |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in su/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 6 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 89                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 2, 4, 8 (Day 14, 28, 56) as Intermediate Study Visits

|                 |                                                                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Conjunctival Fluorescein Staining assessed by NEI scale at Week 2, 4, 8 (Day 14, 28, 56) as Intermediate Study Visits |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.16 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8         |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: NEI scale score               |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Nasal Total Baseline                 | 3.7 (± 2.89)        | 4.2 (± 2.70)      | 5.0 (± 3.27)    |  |
| Nasal Total Week 2                   | 2.1 (± 2.32)        | 3.5 (± 2.53)      | 3.9 (± 3.32)    |  |
| Nasal Total Week 4                   | 2.0 (± 2.23)        | 4.0 (± 2.84)      | 3.7 (± 3.07)    |  |
| Nasal Total Week 8                   | 1.9 (± 2.54)        | 3.3 (± 2.49)      | 3.5 (± 3.49)    |  |
| Temporal Total Baseline              | 3.3 (± 3.15)        | 3.8 (± 2.62)      | 4.5 (± 3.22)    |  |
| Temporal Total Week 2                | 1.9 (± 2.34)        | 2.9 (± 2.46)      | 3.7 (± 3.16)    |  |
| Temporal Total Week 4                | 1.9 (± 2.21)        | 3.0 (± 2.54)      | 3.5 (± 3.17)    |  |
| Temporal Total Week 8                | 1.6 (± 2.48)        | 2.8 (± 2.47)      | 3.2 (± 3.36)    |  |

|                            |                                                                |
|----------------------------|----------------------------------------------------------------|
| Attachments (see zip file) | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 14.2- |
|----------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Statistical analysis title              | Statistical analysis secondary endpoint n. 7 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 89                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Non-Invasive Keratograph Tear Film Break-Up Time at each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84])

|                 |                                                                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Non-Invasive Keratograph Tear Film Break-Up Time at each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.32 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 25

Pro-ocular 1%: 27

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 25

Pro-ocular 1%: 25

Placebo: 29

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 21

Pro-ocular 1%: 24

Placebo: 28

Subjects analysed at 12 weeks:

Pro-ocular 0.5%: 23

Pro-ocular 1%: 26

Placebo: 27

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8, 12     |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: second                        |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 4.2 (± 1.96)        | 5.1 (± 3.26)      | 5.8 (± 4.76)    |  |
| Week 2                               | 6.7 (± 3.76)        | 6.5 (± 4.07)      | 5.8 (± 3.14)    |  |
| Week 4                               | 7.8 (± 4.73)        | 6.2 (± 4.70)      | 5.7 (± 3.35)    |  |
| Week 8                               | 7.2 (± 3.95)        | 5.8 (± 3.56)      | 6.8 (± 4.41)    |  |
| Week 12                              | 6.6 (± 3.53)        | 6.6 (± 4.70)      | 6.1 (± 3.81)    |  |

|                            |                                                          |
|----------------------------|----------------------------------------------------------|
| Attachments (see zip file) | Mean change from Baseline (Visit 1 pre-dose) in No/Table |
|----------------------------|----------------------------------------------------------|

### Statistical analyses

|                            |                                              |
|----------------------------|----------------------------------------------|
| Statistical analysis title | Statistical analysis secondary endpoint n. 8 |
| Comparison groups          | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |

|                                         |               |
|-----------------------------------------|---------------|
| Number of subjects included in analysis | 89            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | < 0.1         |
| Method                                  | ANCOVA        |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Fluorescein Tear Film Break-Up Time at Week 12 (Day 84).

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Fluorescein Tear Film Break-Up Time at Week 12 (Day 84). |
|-----------------|----------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.39 Appendix 16.2 CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:

Pro-ocular 0.5%: 29

Pro-ocular 1%: 30

Placebo: 30

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: | Week 12   |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 24                  | 28                | 27              |  |
| Units: Seconds                       |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 2.3 (± 0.61)        | 2.6 (± 1.12)      | 2.3 (± 1.02)    |  |
| Week 12                              | 3.8 (± 2.55)        | 3.2 (± 2.78)      | 4.2 (± 2.76)    |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in FI/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 9 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo  |
| Number of subjects included in analysis | 79                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.1                                        |
| Method                                  | ANCOVA                                       |

---

**Secondary: Mean change from Baseline (Visit 1 pre-dose) in Tear Meniscus Height at each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84])**

---

|                 |                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Tear Meniscus Height at each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.46 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 27

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 29

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 22

Pro-ocular 1%: 27

Placebo: 28

Subjects analysed at 12 weeks:

Pro-ocular 0.5%: 25

Pro-ocular 1%: 28

Placebo: 27

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8, 12     |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: millimetre(s)                 |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 1.0 (± 4.23)        | 0.3 (± 0.09)      | 0.3 (± 0.11)    |  |
| Week 2                               | 0.3 (± 0.13)        | 0.2 (± 0.07)      | 0.3 (± 0.20)    |  |
| Week 4                               | 1.1 (± 4.10)        | 0.3 (± 0.07)      | 0.3 (± 0.18)    |  |
| Week 8                               | 0.3 (± 0.11)        | 0.3 (± 0.08)      | 0.3 (± 0.16)    |  |
| Week 12                              | 0.3 (± 0.15)        | 0.3 (± 0.10)      | 0.3 (± 0.14)    |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Te/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

## Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 10 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 89                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from Baseline (Visit 0 Screening) in Schirmer's Test at Week 4 (Day 28) and at Week 12 (Day 84).

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 0 Screening) in Schirmer's Test at Week 4 (Day 28) and at Week 12 (Day 84). |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 32 CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:

Pro-ocular 0.5%: 29

Pro-ocular 1%: 30

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

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

End point timeframe:

Week 4, 12

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 25                  | 28                | 27              |  |
| Units: millimetre(s)                 |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 3.2 (± 2.44)        | 3.6 (± 2.59)      | 2.9 (± 1.78)    |  |
| Week 4                               | 4.3 (± 3.20)        | 2.9 (± 2.11)      | 5.6 (± 5.20)    |  |
| Week 12                              | 6.8 (± 7.05)        | 4.6 (± 3.65)      | 5.9 (± 6.45)    |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 0 Screening) in S/Table 32. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b> | Statistical analysis secondary endpoint n. 11 |
| Comparison groups                 | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |

|                                         |                      |
|-----------------------------------------|----------------------|
| Number of subjects included in analysis | 80                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | < 0.1 <sup>[3]</sup> |
| Method                                  | ANCOVA               |

Notes:

[3] - Van-Elteren test (Wilcoxon stratificato) se le assunzioni dell'ANCOVA non erano soddisfatte

## Secondary: Impact of dry eye on quality of life by using Dry Eye-Related Quality-of-Life Scale Questionnaire

|                 |                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------|
| End point title | Impact of dry eye on quality of life by using Dry Eye-Related Quality-of-Life Scale Questionnaire |
|-----------------|---------------------------------------------------------------------------------------------------|

End point description:

Data from Table 34 CSR.

Subjects analysed reported are considered at 12 Weeks.

Subjects analysed at Baseline:

Pro-ocular 0.5%: 29

Pro-ocular 1%: 30

Placebo: 30

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: | Week 12   |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 24                  | 28                | 27              |  |
| Units: Questionnaire score           |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 4.3 (± 1.11)        | 3.6 (± 1.25)      | 4.3 (± 1.15)    |  |
| Week 12                              | 2.9 (± 0.95)        | 3.2 (± 1.03)      | 3.2 (± 0.89)    |  |

|                                   |                                                                 |
|-----------------------------------|-----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Impact of dry eye on quality of life by using Dry /Table 34.pdf |
|-----------------------------------|-----------------------------------------------------------------|

## Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 12 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 79                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

## Secondary: Absolute score of each symptom item in Visual Analogue Scale to each Post-Baseline Visit

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Absolute score of each symptom item in Visual Analogue Scale to each Post-Baseline Visit |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.67 (Sum of all VAS) Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

Subjects analysed at 12 weeks:

Pro-ocular 0.5%: 25

Pro-ocular 1%: 28

Placebo: 27

Subjects analysed at 16 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 27

Placebo: 25

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

End point timeframe:

Week 2, 4, 8, 12,16

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1%   | Placebo             |  |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed          | 29                  | 30                  | 30                  |  |
| Units: VAS score                     |                     |                     |                     |  |
| arithmetic mean (standard deviation) |                     |                     |                     |  |
| Baseline                             | 399.9 (±<br>253.12) | 339.7 (±<br>188.96) | 459.8 (±<br>201.48) |  |
| Week 2                               | 282.5 (±<br>222.91) | 301.2 (±<br>214.92) | 324.7 (±<br>196.73) |  |
| Week 4                               | 290.1 (±<br>210.55) | 288.4 (±<br>203.81) | 282.2 (±<br>181.95) |  |
| Week 8                               | 257.1 (±<br>200.24) | 308.2 (±<br>208.88) | 269.9 (±<br>172.28) |  |
| Week 12                              | 248.8 (±<br>203.55) | 256.1 (±<br>201.27) | 225.9 (±<br>153.77) |  |
| Week 16                              | 220.8 (±<br>175.51) | 259.1 (±<br>195.34) | 217.9 (±<br>163.14) |  |

|                                   |                                                            |
|-----------------------------------|------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Absolute score of each symptom item in Visual /Table 14.2- |
|-----------------------------------|------------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 13 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 89                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Visual Analogue Scale 7 Symptoms items to each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]).

|                 |                                                                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Visual Analogue Scale 7 Symptoms items to each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]). |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.67 (VAS mean) Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

Subjects analysed at 12 weeks:

Pro-ocular 0.5%: 25

Pro-ocular 1%: 28

Placebo: 27

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

End point timeframe:

Week 2, 4, 8, 12

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: VAS scale score               |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 57.2 (± 33.54)      | 48.5 (± 27.03)    | 65.7 (± 28.89)  |  |
| Week 2                               | 40.3 (± 31.89)      | 43.0 (± 30.71)    | 46.5 (± 28.12)  |  |
| Week 4                               | 41.4 (± 29.97)      | 41.1 (± 29.16)    | 40.3 (± 26.00)  |  |
| Week 8                               | 36.7 (± 28.58)      | 44.0 (± 29.79)    | 38.5 (± 24.58)  |  |
| Week 12                              | 35.6 (± 29.04)      | 36.6 (± 28.68)    | 32.3 (± 22.02)  |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Vi/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 14 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 89                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from Baseline (Visit 1 pre-dose) in Corneal Sensitivity to each applicable Post-Baseline Visit (Week 4, 12 [Day 28, 84]).

|                 |                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline (Visit 1 pre-dose) in Corneal Sensitivity to each applicable Post-Baseline Visit (Week 4, 12 [Day 28, 84]). |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.2-2.74 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

Subjects analysed at 12 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 27

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 4, 12           |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 29                  | 30                | 30              |  |
| Units: score                         |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Superior Nasal Baseline              | 4.0 (± 2.57)        | 5.3 (± 1.46)      | 4.0 (± 2.36)    |  |
| Superior Nasal Week 4                | 4.1 (± 2.49)        | 5.4 (± 1.43)      | 4.1 (± 2.41)    |  |
| Superior Nasal Week 12               | 4.1 (± 2.55)        | 5.3 (± 1.52)      | 4.2 (± 2.43)    |  |
| Inferior Nasal Baseline              | 3.9 (± 2.53)        | 5.4 (± 1.46)      | 4.0 (± 2.34)    |  |
| Inferior Nasal Week 4                | 4.1 (± 2.51)        | 5.4 (± 1.45)      | 4.0 (± 2.39)    |  |
| Inferior Nasal Week 12               | 4.0 (± 2.49)        | 5.3 (± 1.53)      | 4.2 (± 2.43)    |  |
| Superior Temporal Baseline           | 4.0 (± 2.54)        | 5.3 (± 1.49)      | 3.9 (± 2.34)    |  |
| Superior Temporal Week 4             | 4.1 (± 2.49)        | 5.4 (± 1.46)      | 4.1 (± 2.41)    |  |
| Superior Temporal Week 12            | 4.1 (± 2.55)        | 5.3 (± 1.52)      | 4.2 (± 2.43)    |  |
| Inferior Temporal Baseline           | 4.0 (± 2.55)        | 5.4 (± 1.46)      | 3.9 (± 2.34)    |  |
| Inferior Temporal Week 4             | 4.1 (± 2.52)        | 5.4 (± 1.45)      | 4.0 (± 2.38)    |  |
| Inferior Temporal Week 12            | 4.0 (± 2.53)        | 5.3 (± 1.52)      | 4.2 (± 2.43)    |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 1 pre-dose) in Co/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 15 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 89                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from Baseline (Visit 0 Screening) in Slit-Lamp Examination to each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]).

|                                                                                                    |                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                    | Mean change from Baseline (Visit 0 Screening) in Slit-Lamp Examination to each applicable Post-Baseline Visit (Week 2, 4, 8, 12 [Day 14, 28, 56, 84]). |
| End point description:                                                                             |                                                                                                                                                        |
| Data from Table 14.2-2.81 Appendix 16.2 CSR. For data spreadsheet, please refer to the attachment. |                                                                                                                                                        |
| End point type                                                                                     | Secondary                                                                                                                                              |
| End point timeframe:                                                                               |                                                                                                                                                        |
| Week 2, 4, 8, 12 (Week 16 follow up included)                                                      |                                                                                                                                                        |

| End point values            | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|-----------------------------|---------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed | 29                  | 30                | 30              |  |
| Units: Subject number       | 29                  | 30                | 30              |  |

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from Baseline (Visit 0 Screening) in S/Table 14.2- |
|-----------------------------------|----------------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 16 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 89                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Local and Systemic adverse events

|                        |                                   |
|------------------------|-----------------------------------|
| End point title        | Local and Systemic adverse events |
| End point description: |                                   |
| Data from Table 54 CSR |                                   |
| End point type         | Secondary                         |
| End point timeframe:   |                                   |
| Full trial duration    |                                   |

| End point values            | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|-----------------------------|---------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed | 31                  | 30                | 30              |  |
| Units: Number of events     |                     |                   |                 |  |
| Local                       | 10                  | 6                 | 2               |  |
| Systemic                    | 13                  | 10                | 6               |  |

|                                   |                                                |
|-----------------------------------|------------------------------------------------|
| <b>Attachments (see zip file)</b> | Local and Systemic adverse events/Table 54.pdf |
|-----------------------------------|------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence and frequency of Treatment-emergent adverse events

**(TEAEs) at any time during the study.**

|                         |                                                                                                    |
|-------------------------|----------------------------------------------------------------------------------------------------|
| End point title         | Incidence and frequency of Treatment-emergent adverse events (TEAEs) at any time during the study. |
| End point description:  |                                                                                                    |
| Data from Table 55 CSR. |                                                                                                    |
| End point type          | Secondary                                                                                          |
| End point timeframe:    |                                                                                                    |
| Full trial duration     |                                                                                                    |

| End point values            | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|-----------------------------|---------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed | 31                  | 30                | 30              |  |
| Units: Number of events     |                     |                   |                 |  |
| Mild                        | 20                  | 13                | 5               |  |
| Moderate                    | 2                   | 3                 | 1               |  |
| Severe                      | 1                   | 0                 | 1               |  |

|                                   |                                                                                                    |
|-----------------------------------|----------------------------------------------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Incidence and frequency of Treatment-emergent adverse events (TEAEs) at any time during the study. |
|-----------------------------------|----------------------------------------------------------------------------------------------------|

**Statistical analyses**

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 18 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 91                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           |                                               |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

**Secondary: Serum progesterone determination**

|                                                                                                  |                                  |
|--------------------------------------------------------------------------------------------------|----------------------------------|
| End point title                                                                                  | Serum progesterone determination |
| End point description:                                                                           |                                  |
| Data from Table 59 CSR.                                                                          |                                  |
| In categories:                                                                                   |                                  |
| NOR = normal                                                                                     |                                  |
| AB NCS = abnormal Not Clinically Significant                                                     |                                  |
| AB CS = abnormal Clinically Significant                                                          |                                  |
| MIS = Missing                                                                                    |                                  |
| End point type                                                                                   | Secondary                        |
| End point timeframe:                                                                             |                                  |
| Pre-randomisation and Randomisation (RAN), Week 4 (W4), Week 12 (W12) and Early Termination (ET) |                                  |

| End point values            | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|-----------------------------|---------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed | 31                  | 30                | 30              |  |
| Units: Number of patients   |                     |                   |                 |  |
| RAN NOR                     | 30                  | 28                | 30              |  |
| RAN AB NCS                  | 0                   | 1                 | 0               |  |
| RAN AB CS                   | 0                   | 0                 | 0               |  |
| RAN MIS                     | 1                   | 1                 | 0               |  |
| W4 NOR                      | 27                  | 24                | 28              |  |
| W4 AB NCS                   | 0                   | 1                 | 1               |  |
| W4 AB CS                    | 0                   | 0                 | 0               |  |
| W4 MIS                      | 2                   | 4                 | 1               |  |
| W12 NOR                     | 23                  | 26                | 26              |  |
| W12 AB NCS                  | 0                   | 2                 | 1               |  |
| W12 AB CS                   | 0                   | 0                 | 0               |  |
| W12 MIS                     | 3                   | 0                 | 0               |  |
| ET NOR                      | 0                   | 0                 | 0               |  |
| ET AB NCS                   | 0                   | 0                 | 0               |  |
| ET AB CS                    | 0                   | 0                 | 0               |  |
| ET MIS                      | 0                   | 0                 | 0               |  |

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| <b>Attachments (see zip file)</b> | Serum progesterone determination/Table 59.pdf |
|-----------------------------------|-----------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change from baseline (Visit 1 pre-dose) in Intraocular Pressure at each applicable post-baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)].

|                 |                                                                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline (Visit 1 pre-dose) in Intraocular Pressure at each applicable post-baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)]. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.3.5-1.1 Appendix 16.2 CSR.

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28  
Placebo: 28

Subjects analysed at 12 weeks:  
Pro-ocular 0.5%: 25  
Pro-ocular 1%: 28  
Placebo: 27

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8, 12     |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 31                  | 30                | 30              |  |
| Units: mmHg                          |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 13.5 (± 2.20)       | 14.5 (± 1.81)     | 14.2 (± 1.97)   |  |
| Week 2                               | 13.8 (± 1.40)       | 14.4 (± 1.64)     | 14.4 (± 2.30)   |  |
| Week 4                               | 13.1 (± 1.74)       | 13.8 (± 1.94)     | 14.4 (± 1.35)   |  |
| Week 8                               | 13.5 (± 1.53)       | 14.5 (± 1.93)     | 14.8 (± 3.01)   |  |
| Week 12                              | 13.8 (± 1.41)       | 13.7 (± 2.03)     | 13.8 (± 1.93)   |  |

|                            |                                                          |
|----------------------------|----------------------------------------------------------|
| Attachments (see zip file) | Mean change from baseline (Visit 1 pre-dose) in In/Table |
|----------------------------|----------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| Statistical analysis title              | Statistical analysis secondary endpoint n. 20 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 91                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from baseline (Visit 0 Screening) in Undilated Fundoscopy Examination at Week 12 (Day 84).

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline (Visit 0 Screening) in Undilated Fundoscopy Examination at Week 12 (Day 84). |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.3.5-1.3

In categories:

N = Normal

ANCS = Abnormal Not Clinically Significant

ACS = Abnormal Clinically Significant

M = Missing

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values            | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|-----------------------------|---------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed | 31                  | 30                | 30              |  |
| Units: Number of subjects   |                     |                   |                 |  |
| Vitreous Week 12 N          | 24                  | 28                | 26              |  |
| Vitreous Week 12 ANCS       | 0                   | 0                 | 1               |  |
| Vitreous Week 12 ACS        | 0                   | 0                 | 0               |  |
| Vitreous Week 12 M          | 2                   | 0                 | 0               |  |
| Retina/Macula Week 12 N     | 24                  | 28                | 26              |  |
| Retina/Macula Week 12 ANCS  | 0                   | 0                 | 1               |  |
| Retina/Macula Week 12 ACS   | 0                   | 0                 | 0               |  |
| Retina/Macula Week 12 M     | 2                   | 0                 | 0               |  |
| Choroid Week 12 N           | 24                  | 28                | 26              |  |
| Choroid Week 12 ANCS        | 0                   | 0                 | 1               |  |
| Choroid Week 12 ACS         | 0                   | 0                 | 0               |  |
| Choroid Week 12 M           | 2                   | 0                 | 0               |  |
| Optic Nerve Week 12 N       | 24                  | 28                | 26              |  |
| Optic Nerve Week 12 ANCS    | 0                   | 0                 | 1               |  |
| Optic Nerve Week 12 ACS     | 0                   | 0                 | 0               |  |
| Optic Nerve Week 12 M       | 2                   | 0                 | 0               |  |
| Cup/Disc Ratio Week 12 N    | 24                  | 27                | 26              |  |
| Cup/Disc Ratio Week 12 ANCS | 0                   | 0                 | 1               |  |
| Cup/Disc Ratio Week 12 ACS  | 0                   | 1                 | 0               |  |
| Cup/Disc Ratio Week 12 M    | 2                   | 0                 | 0               |  |

|                                   |                                                          |
|-----------------------------------|----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from baseline (Visit 0 Screening) in U/Table |
|-----------------------------------|----------------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from baseline (Visit 1 pre-dose) in BCVA at each applicable post- baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)].

|                 |                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline (Visit 1 pre-dose) in BCVA at each applicable post- baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)]. |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Data from Table 14.3.5-1.5

Subjects analysed reported are considered at Baseline.

Subjects analysed at 2 Weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 28

Placebo: 30

Subjects analysed at 4 weeks:

Pro-ocular 0.5%: 28

Pro-ocular 1%: 29

Placebo: 30

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 28

Subjects analysed at 8 weeks:

Pro-ocular 0.5%: 24

Pro-ocular 1%: 28

Placebo: 27

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 2, 4, 8, 12     |           |

| End point values                     | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|--------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                   | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed          | 31                  | 30                | 30              |  |
| Units: Score                         |                     |                   |                 |  |
| arithmetic mean (standard deviation) |                     |                   |                 |  |
| Baseline                             | 0.07 (± 0.122)      | 0.04 (± 0.122)    | 0.03 (± 0.096)  |  |
| Week 2                               | 0.08 (± 0.129)      | -0.54 (± 3.035)   | 0.03 (± 0.095)  |  |
| Week 4                               | 0.07 (± 0.106)      | 0.04 (± 0.126)    | 0.02 (± 0.095)  |  |
| Week 8                               | 0.09 (± 0.161)      | 0.06 (± 0.145)    | 0.02 (± 0.101)  |  |
| Week 12                              | 0.06 (± 0.113)      | 0.06 (± 0.136)    | 0.04 (± 0.151)  |  |

|                            |                                                          |
|----------------------------|----------------------------------------------------------|
| Attachments (see zip file) | Mean change from baseline (Visit 1 pre-dose) in BC/Table |
|----------------------------|----------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| Statistical analysis title              | Statistical analysis secondary endpoint n. 22 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 91                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

### Secondary: Mean change from baseline (Visit 0 Screening) in Meiboscore grading at Week 12 (Day 84).

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline (Visit 0 Screening) in Meiboscore grading at Week 12 (Day 84). |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

Data from Table 67 CSR.

0 = No loss of meibomian glands

1 = Loss of less than 1/3 of the total meibomian gland area

2 = Loss of 1/3 to 2/3 of the total area

3 = Loss of more than 2/3 of the area

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

End point timeframe:

Week 12

| End point values                   | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                 | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed        | 31                  | 30                | 30              |  |
| Units: Score of Meiboscore Grading |                     |                   |                 |  |
| Screening 0                        | 6                   | 13                | 6               |  |
| Screening 1                        | 8                   | 6                 | 3               |  |
| Screening 2                        | 13                  | 9                 | 15              |  |
| Screening 3                        | 4                   | 2                 | 6               |  |
| Week 12 0                          | 6                   | 11                | 4               |  |
| Week 12 1                          | 11                  | 11                | 7               |  |
| Week 12 2                          | 5                   | 6                 | 14              |  |
| Week 12 3                          | 2                   | 0                 | 2               |  |
| Missing                            | 2                   | 0                 | 0               |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from baseline (Visit 0 Screening) in M/Table 67. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis secondary endpoint n. 23 |
| Comparison groups                       | Pro-ocular™ 0.5% v Pro-ocular™ 1% v Placebo   |
| Number of subjects included in analysis | 91                                            |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | < 0.1                                         |
| Method                                  | ANCOVA                                        |

**Secondary: Mean change from baseline (Visit 1 pre-dose) in (Keratography) Conjunctival Hyperemia score to each applicable post-baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)].**

|                 |                                                                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline (Visit 1 pre-dose) in (Keratography) Conjunctival Hyperemia score to each applicable post-baseline visit [Week 2, 4, 8, 12 (Day 14, 28, 56, 84)]. |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

0 = None  
1 = Mild  
2 = Moderate  
3 = Severe  
Missing

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

End point timeframe:

Data from Table 69 CSR.

Randomisation, pre-randomisation  
Randomisation, post-randomisation  
Week 2  
Week 4  
Week 8  
Week 12

| End point values                             | Pro-ocular™<br>0.5% | Pro-ocular™<br>1% | Placebo         |  |
|----------------------------------------------|---------------------|-------------------|-----------------|--|
| Subject group type                           | Reporting group     | Reporting group   | Reporting group |  |
| Number of subjects analysed                  | 31                  | 30                | 30              |  |
| Units: Number of patients                    |                     |                   |                 |  |
| Randomisation, pre-randomisation 0           | 0                   | 0                 | 1               |  |
| Randomisation, pre-randomisation 1           | 13                  | 11                | 11              |  |
| Randomisation, pre-randomisation 2           | 14                  | 15                | 16              |  |
| Randomisation, pre-randomisation 3           | 4                   | 3                 | 1               |  |
| Randomisation, pre-randomisation<br>Missing  | 0                   | 0                 | 1               |  |
| Randomisation, post-randomisation 0          | 0                   | 0                 | 1               |  |
| Randomisation, post-randomisation 1          | 15                  | 13                | 13              |  |
| Randomisation, post-randomisation 2          | 10                  | 13                | 13              |  |
| Randomisation, post-randomisation 3          | 5                   | 2                 | 1               |  |
| Randomisation, post-randomisation<br>Missing | 1                   | 0                 | 2               |  |
| Week 2 0                                     | 0                   | 0                 | 1               |  |
| Week 2 1                                     | 15                  | 13                | 18              |  |
| Week 2 2                                     | 9                   | 12                | 11              |  |
| Week 2 3                                     | 3                   | 3                 | 0               |  |
| Week 2 Missing                               | 2                   | 0                 | 0               |  |
| Week 4 0                                     | 0                   | 0                 | 0               |  |
| Week 4 1                                     | 12                  | 12                | 16              |  |
| Week 4 2                                     | 14                  | 14                | 11              |  |
| Week 4 3                                     | 1                   | 2                 | 2               |  |
| Week 4 Missing                               | 1                   | 1                 | 1               |  |
| Week 8 0                                     | 0                   | 0                 | 1               |  |
| Week 8 1                                     | 11                  | 10                | 13              |  |
| Week 8 2                                     | 10                  | 12                | 13              |  |
| Week 8 3                                     | 1                   | 4                 | 1               |  |
| Week 8 Missing                               | 5                   | 2                 | 0               |  |
| Week 12 0                                    | 0                   | 0                 | 0               |  |
| Week 12 1                                    | 14                  | 13                | 12              |  |
| Week 12 2                                    | 7                   | 10                | 13              |  |
| Week 12 3                                    | 2                   | 4                 | 2               |  |

|                 |   |   |   |  |
|-----------------|---|---|---|--|
| Week 12 Missing | 2 | 0 | 0 |  |
|-----------------|---|---|---|--|

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Mean change from baseline (Visit 1 pre-dose) in (K/Table 69. |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The safety evaluation will cover the collection of adverse events since the signature of the Informed Consent Form by each patient to the end of the study and follow up.

Adverse event reporting additional description:

All non-serious adverse events were reported regardless of frequency.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Pro-ocular™ 0.5% |
|-----------------------|------------------|

Reporting group description:

Pro-ocular™ 0.5% topical gel (0.35 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Pro-ocular™ 1% |
|-----------------------|----------------|

Reporting group description:

Pro-ocular™ 1% topical gel (0.7 mg progesterone/dose, BID to forehead for 12 weeks) was tested in adults with moderate to severe dry eye.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo topical gel (no active ingredient; titanium dioxide instead of progesterone), identical in appearance and dosing to active gel (0.07g BID to forehead for 12 weeks).

| Serious adverse events                                              | Pro-ocular™ 0.5% | Pro-ocular™ 1% | Placebo        |
|---------------------------------------------------------------------|------------------|----------------|----------------|
| Total subjects affected by serious adverse events                   |                  |                |                |
| subjects affected / exposed                                         | 1 / 31 (3.23%)   | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| number of deaths (all causes)                                       | 0                | 0              | 0              |
| number of deaths resulting from adverse events                      |                  |                |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                |                |
| Acute myeloid leukaemia                                             |                  |                |                |
| subjects affected / exposed                                         | 1 / 31 (3.23%)   | 0 / 30 (0.00%) | 0 / 30 (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: 0 %

| <b>Non-serious adverse events</b>                     | Pro-ocular™ 0.5% | Pro-ocular™ 1%  | Placebo         |
|-------------------------------------------------------|------------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                  |                 |                 |
| subjects affected / exposed                           | 13 / 31 (41.94%) | 8 / 30 (26.67%) | 6 / 30 (20.00%) |
| Nervous system disorders                              |                  |                 |                 |
| Headache                                              |                  |                 |                 |
| subjects affected / exposed                           | 2 / 31 (6.45%)   | 2 / 30 (6.67%)  | 2 / 30 (6.67%)  |
| occurrences (all)                                     | 1                | 2               | 3               |
| Eye disorders                                         |                  |                 |                 |
| Ocular discomfort                                     |                  |                 |                 |
| subjects affected / exposed                           | 13 / 31 (41.94%) | 8 / 30 (26.67%) | 6 / 30 (20.00%) |
| occurrences (all)                                     | 22               | 16              | 8               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 September 2021 | <p>The most substantial change between Version 1.0 (July 2019) and Version 2.0 (September 2021) involves the addition of exploratory objectives and endpoints. Version 2.0 introduces a combined eye analysis examining both eyes simultaneously, rather than focusing solely on the "worst eye." Furthermore, direct comparisons between the two progesterone concentrations (0.5% vs 1.0%) were added as exploratory endpoints. To accommodate the combined eye analysis, Version 2.0 incorporates a Mixed Model Repeated Measures (MMRM) approach, which accounts for within-subject correlation between both eyes. Moreover, TearScan Grading was completely removed from the assessment schedule, eliminating associated procedures from all study visits. Finally, the study timeline was delayed, with the start moved from Q4 2019 to Q1 2021, and expected completion shifted from Q2 2020 to Q1 2022. Reflecting updated regulatory requirements, Version 2.0 includes references to EU Regulation 536/2014 regarding document retention requirements. In summary, the amendment maintains all primary and secondary objectives unchanged while substantially enriching the exploratory research potential through bilateral eye analysis and direct dose comparison.</p> |

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.

Study was interrupted at 91 randomized patients, due to a very slow and difficult recruitment lower dropout rate than planned. Even with 91 randomized, the power was 80% so fully acceptable from a statistical point of view.

Notes: