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,
Public contact	LAURA BONINO, SOCIETA' INDUSTRIA FARMACEUTICA ITALIANA (SIFI) s.p.a, clinicaldevelopment@sifigroup.com
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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 ≥18, dry eye ≥3 months, NEI >3, TBUT ≤5s, Schirmer's 1–10

Pre-assignment period milestones

Number of subjects started	96[1]
Number of subjects completed	91

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Lost to Follow Up: 1
Reason: Number of subjects	Consent withdrawn by subject: 3
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

Arm title	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

Arm title	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

Number of subjects in period 1	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 More Than Twice A Week			
Units: Subjects			
Yes	0	0	0
No	31	30	30
Use of Sunscreen on The Forehead or 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

Reporting group values	Total		
Number of subjects	91		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	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:	
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).	

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:	
Data from Table 15 CSR	
End point type	Primary
End point timeframe:	
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)	

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

Statistical analyses

Statistical analysis title	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 [1]
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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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 [2]
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

	Fluorescein Staining assessed by NEI scale at Week 12 (Day 84).

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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 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 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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

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 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)	

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. 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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 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 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™ 0.5%	Pro-ocular™ 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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

Attachments (see zip file)	Mean change from Baseline (Visit 0 Screening) in S/Table 32.

Statistical analyses

Statistical analysis title	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 [3]
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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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 (± 253.12)	339.7 (± 188.96)	459.8 (± 201.48)	
Week 2	282.5 (± 222.91)	301.2 (± 214.92)	324.7 (± 196.73)	
Week 4	290.1 (± 210.55)	288.4 (± 203.81)	282.2 (± 181.95)	
Week 8	257.1 (± 200.24)	308.2 (± 208.88)	269.9 (± 172.28)	
Week 12	248.8 (± 203.55)	256.1 (± 201.27)	225.9 (± 153.77)	
Week 16	220.8 (± 175.51)	259.1 (± 195.34)	217.9 (± 163.14)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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)	

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. 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™ 0.5%	Pro-ocular™ 1%	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	30	30	
Units: Subject number	29	30	30	

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

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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	

Attachments (see zip file)	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™ 0.5%	Pro-ocular™ 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	

Attachments (see zip file)	Incidence and frequency of Treatment-emergent adve/Table

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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	

Attachments (see zip file)	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™ 0.5%	Pro-ocular™ 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™ 0.5%	Pro-ocular™ 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	

Attachments (see zip file)	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™ 0.5%	Pro-ocular™ 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™ 0.5%	Pro-ocular™ 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	

Attachments (see zip file)	Mean change from baseline (Visit 0 Screening) in M/Table 67.

Statistical analyses

Statistical analysis title	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™ 0.5%	Pro-ocular™ 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 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 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	

Attachments (see zip file)	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 %

Non-serious adverse events	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	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.

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: