Clinical trial results:
An open-label study evaluating safety and efficacy of recombinant human nerve growth factor (rhNGF) eye drops at different doses in patients with Dry Eye

Summary

EudraCT number	2013-004271-12
Trial protocol	AT
Global end of trial date	30 January 2015

Results information

Result version number	v1 (current)
This version publication date	02 October 2016
First version publication date	02 October 2016

Trial information

Trial identification

Sponsor protocol code	NGF0213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02101281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici spa
Sponsor organisation address	Via Santa Lucia 6, Milano, Italy, 20122
Public contact	Medical Expert, Dompé farmaceutici spa, +39 02583831, flavio.mantelli@dompe.com
Scientific contact	Medical Expert, Dompé farmaceutici spa, +39 02583831, flavio.mantelli@dompe.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2015
Global end of trial reached?	Yes
Global end of trial date	30 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy and safety of different doses of rhNGF when administered as eye drops to patients with Dry Eye.
on the basis of the following assessments:
- Symptom Assessment in Dry Eye (SANDE)
- Ocular surface vital staining (National Eye Institute [NEI] scales)
- Schirmer test type I (without anaesthesia)
performed on days 1, 8±1, 29±1 and 56±4. Changes from baseline (screening visit) will be evaluated.
- Treatment-emergent adverse events (TEAEs), assessed throughout the study

Protection of trial subjects:

The study protocol final version 2.0, 10JAN14, the Investigator's brochure and all other relevant documentation were reviewed and approved by an independent Ethics Committee (Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeines Krankenhauses der Stadt Wien AKH", Vienna; Appendix 16.1.3) on 20JAN14. Ref. nr. 2029/2013.

The study was performed in accordance with the relevant guidelines and the Declaration of Helsinki. The present clinical trial was carried out according to the general principles of: "ICH Harmonised Tripartite Guidelines for Good Clinical Practice "ICH Topic E6, CPMP/ICH/135/95, July 1996 including post Step 4 errata, status September 1997 and post Step 5 errata (linguistic corrections), July 2002.

Before being admitted to the clinical study, subjects expressed their consent to participate. The investigator explained the nature, scope and possible consequences of the clinical study in an understandable form. Information was provided to the subjects in both oral and written form.
Each patient received a copy of the written informed consent form, signed by them and the investigator.

Background therapy:

Required use of artificial tears for the treatment of dry eye within the 3 months prior to study enrolment.
Current use or recommended use of artificial tears for the treatment of dry eye.

Evidence for comparator:

N.A.

Actual start date of recruitment	24 March 2014
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	Austria: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	34
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients have been recruited in Department of Clinical Pharmacology, Medical University and General Hospital of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria. The date of first enrolment was on 24 March 2014 and the last vol. completed on 30 January 2015.

Pre-assignment

Screening details:

All patients are screened basing on the inclusion and exclusion criteria and than enrolled.

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Group 1: rhNGF 20 µg/mL: One drop (35 µL) corresponding to 0.70 µg of rhNGF was instilled into each eye twice a day (b.i.d.) every 12±2 h for a total daily dose of 2.8 µg (both eyes), for 28 consecutive days. Total dose was 78.4 µg/28 days. Batch: f14131; expiry: OCT14.
At the end of the 1st study part (Group 1), the primary efficacy and safety parameters were analysed. Dose escalation proceeded with Group 2 since there were no safety findings that could pose unacceptable risks to patients. In detail, the study continued with the dose of 4 µg/mL since at least 2 out of the 3 primary efficacy parameters improved in Group 1.

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

Dosage and administration details:

One drop (35 µL) corresponding to 0.70 µg of rhNGF was instilled into each eye twice a day (b.i.d.) every 12±2 h for a total daily dose of 2.8 µg (both eyes), for 28 consecutive days.Total dose was 78.4 µg/28 days.

Arm title	Group 2

Arm description:

Group 2: rhNGF 4 µg/mL: One drop (35 µL) corresponding to 0.14 µg of rhNGF was instilled into each eye b.i.d. every 12±2 h for a total daily dose of 0.56 µg, for 28 consecutive days. Total dose was 15.68 µg/28 days.

Arm type	Experimental

Investigational medicinal product name	rhNGF 4 µg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (35 µL) corresponding to 0.14 µg of rhNGF was instilled into each eye b.i.d. every 12±2 h for a total daily dose of 0.56 µg, for 28 consecutive days. Total dose was 15.68 µg/28 days

Number of subjects in period 1	Group 1	Group 2
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Group 1: rhNGF 20 µg/mL: One drop (35 µL) corresponding to 0.70 µg of rhNGF was instilled into each eye twice a day (b.i.d.) every 12±2 h for a total daily dose of 2.8 µg (both eyes), for 28 consecutive days. Total dose was 78.4 µg/28 days. Batch: f14131; expiry: OCT14. At the end of the 1st study part (Group 1), the primary efficacy and safety parameters were analysed. Dose escalation proceeded with Group 2 since there were no safety findings that could pose unacceptable risks to patients. In detail, the study continued with the dose of 4 µg/mL since at least 2 out of the 3 primary efficacy parameters improved in Group 1.	
Reporting group title	Group 2
Reporting group description:	
Group 2: rhNGF 4 µg/mL: One drop (35 µL) corresponding to 0.14 µg of rhNGF was instilled into each eye b.i.d. every 12±2 h for a total daily dose of 0.56 µg, for 28 consecutive days. Total dose was 15.68 µg/28 days.	

Reporting group values	Group 1	Group 2	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	18	14	32
From 65-84 years	2	6	8
85 years and over	0	0	0
Age continuous			
Male and female patients ≥18 year old with dry eye syndrome. Patients with severe dry eye due to primary or secondary Sjogren`s syndrome (due to polyarthritis) or a graft versus host disease (GvHD) and diabetes etc. could be included in the study. For each treatment group not less than 6 subjects had a severe dry eye condition according to the Report of the International Dry Eye Workshop (DEWS), 2007 (2).			
Units: years			
arithmetic mean	48.4	55.9	
standard deviation	± 12	± 14.8	-
Gender categorical Units: Subjects			
Female	16	17	33
Male	4	3	7

Subject analysis sets	
Subject analysis set title	FAS (symptoms assessment in dry eye,gruppo 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): all enrolled patients who received at least one dose of the IMP L . This analysis set was used for the efficacy analysis. Group 1: rhNGF 20 µg/mL	
Subject analysis set title	PP (Symptom assessment in dry eye gruppo 1)
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol set (PP): all enrolled patients who received at least one dose of the IMP fulfilled the study protocol requirements in terms of IMP intake and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the efficacy analysis. Group 2 : rhNGF 20 µg/m	

Subject analysis set title	FAS (Symptom assessment in dry eye gruppo 2)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): all enrolled patients who received at least one dose of the IMP. This analysis set was used for the efficacy analysis. Group 2 : rhNGF 4 µg/mL

Subject analysis set title	PP (Symptom assessment in dry eye gruppo2)
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol set (PP): all enrolled patients who fulfilled the study protocol requirements in terms of IMP intake and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the efficacy analysis.
Group 2 : rhNGF 4 µg/mL

Reporting group values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)
Number of subjects	20	14	20
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Male and female patients ≥18 year old with dry eye syndrome. Patients with severe dry eye due to primary or secondary Sjogren`s syndrome (due to polyarthritis) or a graft versus host disease (GvHD) and diabetes etc. could be included in the study. For each treatment group not less than 6 subjects had a severe dry eye condition according to the Report of the International Dry Eye Workshop (DEWS), 2007 (2).			
Units: years arithmetic mean standard deviation	 48.4 ± 12	 46.9 ± 11.4	 55.9 ± 14.8
Gender categorical Units: Subjects			
Female Male	16 4	11 3	17 3

Reporting group values	PP (Symptom assessment in dry eye gruppo2)		
Number of subjects	16		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Male and female patients ≥18 year old with dry eye syndrome. Patients with severe dry eye due to primary or secondary Sjogren`s syndrome (due to polyarthritis) or a graft versus host disease (GvHD) and diabetes etc. could be included in the study. For each treatment group not less than 6 subjects had a severe dry eye condition according to the Report of the International Dry Eye Workshop (DEWS), 2007 (2).			
Units: years arithmetic mean standard deviation	 56.3 ± 13.4		

Gender categorical Units: Subjects			
Female	14		
Male	2		

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Group 1: rhNGF 20 µg/mL: One drop (35 µL) corresponding to 0.70 µg of rhNGF was instilled into each eye twice a day (b.i.d.) every 12±2 h for a total daily dose of 2.8 µg (both eyes), for 28 consecutive days. Total dose was 78.4 µg/28 days. Batch: f14131; expiry: OCT14.
At the end of the 1st study part (Group 1), the primary efficacy and safety parameters were analysed. Dose escalation proceeded with Group 2 since there were no safety findings that could pose unacceptable risks to patients. In detail, the study continued with the dose of 4 µg/mL since at least 2 out of the 3 primary efficacy parameters improved in Group 1.

Reporting group title	Group 2

Reporting group description:

Group 2: rhNGF 4 µg/mL: One drop (35 µL) corresponding to 0.14 µg of rhNGF was instilled into each eye b.i.d. every 12±2 h for a total daily dose of 0.56 µg, for 28 consecutive days. Total dose was 15.68 µg/28 days.

Subject analysis set title	FAS (symptoms assessment in dry eye,gruppo 1)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): all enrolled patients who received at least one dose of the IMP L . This analysis set was used for the efficacy analysis. Group 1: rhNGF 20 µg/mL

Subject analysis set title	PP (Symptom assessment in dry eye gruppo 1)
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol set (PP): all enrolled patients who received at least one dose of the IMP fulfilled the study protocol requirements in terms of IMP intake and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the efficacy analysis. Group 2 : rhNGF 20 µg/m

Subject analysis set title	FAS (Symptom assessment in dry eye gruppo 2)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): all enrolled patients who received at least one dose of the IMP. This analysis set was used for the efficacy analysis. Group 2 : rhNGF 4 µg/mL

Subject analysis set title	PP (Symptom assessment in dry eye gruppo2)
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol set (PP): all enrolled patients who fulfilled the study protocol requirements in terms of IMP intake and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the efficacy analysis.
Group 2 : rhNGF 4 µg/mL

Primary: Symptom assessment in dry eye (SANDE)

End point title	Symptom assessment in dry eye (SANDE)

End point description:

The SANDE questionnaire was a short questionnaire to evaluate both dry eye intensity and frequency by using a 100-mm VAS. The patient symptoms of ocular dryness and/or irritation were quantified on the scale based on two questions that inquired about both severity and frequency of symptoms. The patients evaluated their symptoms using the VAS giving the value they were feeling from none to an extreme value. Each VAS value was measured in millimetres from the left end of the line to each patient's mark. The question about symptom severity and the question about symptom irritation were evaluated through 2 distinct 100-mm VAS.
VAS values of SANDE and their changes from baseline are listed and summarised using descriptive statistics by dose group, disease severity at screening and evaluation visit.
VAS values of SANDE were compared within dose group, disease severity and evaluation visit versus their baseline values by a two-sided Wilcoxon signed-rank test with a nominal α level of 0.05

End point type	Primary

End point timeframe:

visit 1 (Screening day-15 up to day-1), visit 2 (day 1), visit 3(day 1 to day 7+-1), visit 6 (day 29+-1) and final visit(visit 7, day 54+-4 /EVT)

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: 100 mm VAS				
arithmetic mean (standard deviation)				
overall visit 1-frequency	55.3 (± 27.3)	56.6 (± 29.2)	59.7 (± 29.2)	50.6 (± 25.2)
overall visit 2-frequency	47.3 (± 24.2)	45.1 (± 24.8)	49.7 (± 22.4)	45.8 (± 21)
overall visit 3-frequency	40.3 (± 23.1)	39.4 (± 22.3)	36.4 (± 23.8)	32.3 (± 24.9)
overall visit 6-frequency	28.4 (± 26.2)	27.1 (± 25.3)	33.5 (± 26.4)	28.4 (± 23.1)
overall final visit-frequency	25.2 (± 26.5)	26.9 (± 26.8)	31.7 (± 26.8)	23.3 (± 22)
overall visit 1-severity	52.8 (± 23.2)	54.1 (± 23.3)	60.1 (± 29.6)	54.1 (± 28.7)
overall visit 2-severity	45.3 (± 23.7)	43.1 (± 23.8)	50.3 (± 21.6)	46.9 (± 21.9)
overall visit 3-severity	41.1 (± 23.1)	39.6 (± 22.2)	39.1 (± 27)	33.5 (± 26.6)
overall visit 6-severity	25.9 (± 26.9)	24.7 (± 25.7)	31.5 (± 25.5)	26.9 (± 21.7)
overall final visit-severity	23.9 (± 28.1)	25.8 (± 28.1)	31.9 (± 27.9)	22.4 (± 20.9)

Attachments (see zip file)	End Point/Symptom assessment in dry eye (SANDE).pdf

Statistical analyses

Statistical analysis title	Symptom assessment in dry eye-SANDE, Full analysis

Statistical analysis description:

VAS values of symptom assessment in dry eye and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.1

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	81
Variability estimate	Standard deviation
Dispersion value	26.5

Primary: Ocular surface vital staining with lissamine green (LG) (National Eye Institute [NEI] scales)

End point title	Ocular surface vital staining with lissamine green (LG) (National Eye Institute [NEI] scales)

End point description:

LG impregnated paper strips (EasyOpht, Italy) containing 1.5 mg of the dye were used to detect conjunctival and corneal epithelial defects. As grading scale of the corneal and conjunctival damage, the NEI/Industry Workshop guideline was used. The cornea was divided into five sectors (central, superior, inferior, nasal and temporal), each of which was scored on a scale of 0–3, with a maximal global score of 15. Both nasally and temporally, the conjunctiva was divided into a superior paralimbal area, an inferior paralimbal area and a peripheral area with a grading scale of 0–3 and with a maximal score of 9 for the nasal and temporal conjunctiva. Before placing the strip in the lower fornix of the eye, a drop of sterile saline was added to the strip.

End point type	Primary

End point timeframe:

visit 1 (Screening day-15 up to day-1), visit 2 (day 1), visit 3(day 1 to day 7+-1), visit 6 (day 29+-1) and final visit(visit 7, day 54+-4 /EVT)

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	20	20
Units: millimeter(s)				
arithmetic mean (standard deviation)				
overall visit 2-study eye	11.8 (± 3.5)	11.9 (± 3.6)	12.9 (± 5.4)	12 (± 4)
overall visit 3-study eye	7.4 (± 2.8)	7.6 (± 3.1)	10.4 (± 5.5)	9.2 (± 4.4)
overall visit 6-study eye	3.8 (± 3.1)	3.9 (± 3.3)	7.5 (± 4.8)	7.2 (± 4.6)
overall final visit -study eye	5.5 (± 3.2)	6.1 (± 3.5)	7.7 (± 5.3)	7.1 (± 5.3)
overall visit 2- non study eye	10.3 (± 4.1)	9.9 (± 4.4)	9.1 (± 6.1)	8.1 (± 4)
overall visit 3- non study eye	7.3 (± 3.9)	7.4 (± 3.3)	9.3 (± 6.1)	8.1 (± 5.2)
overall visit 6- non study eye	4.1 (± 3.6)	4.2 (± 3.3)	7.6 (± 5.7)	7.1 (± 5.6)
overall final visit - non study eye	5 (± 4.4)	5.2 (± 4.7)	7.3 (± 5.5)	6.9 (± 5.7)

Attachments (see zip file)	End Point/Ocular surface staining with lissamine green.pdf

Statistical analyses

Statistical analysis title	Ocular surface staining with Lissamine green [NEI]

Statistical analysis description:

Ocular surface staining with Lissamine green scores, total corneal staining score, total conjunctival staining score and total staining score and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	6
Variability estimate	Standard deviation
Dispersion value	1.6

Primary: Schirmer test type I (without anaesthesia)

End point title	Schirmer test type I (without anaesthesia)

End point description:

Schirmer plus® strips (Gecis, France) were used. This test was performed to measure aqueous tear secretion prior to the instillation of any dilating or anaesthetic eye drops. Both eyes could be tested at the same time. While the patient was looking upwards, the lower lid was drawn gently downwards and temporarily. The rounded bent end of a sterile strip was inserted into the lower conjunctival sac over the temporal one-third of the lower eyelid margin, without touching directly the Schirmer test strip with the fingers.After 5 min, the Schirmer test strip was removed and the length of the tear absorption on the strip was measured (millimeters/5 min). The wetting distance at 5 min for each eye was recorded. Values of Schirmer's test type I (i.e. tear wetting distance at 5 min) and their changes from baseline (screening visit) are summarised by eye (study eye and non study eye) and evaluation visit and stratified by severity level.

End point type	Primary

End point timeframe:

visit 1(screening day -15 up to day -1), visit 2 (day 1), visit 3 (day 8+-1), visit 6 (day 29+-1), final visit(visit 7, day 56+-4/ETV)

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: mm/ 5minuti				

arithmetic mean (standard deviation)				
overall Visit 2 - Study Eye	5.4 (± 5.7)	5.4 (± 5.7)	6.5 (± 6.7)	7.3 (± 7.2)
overall Visit 3 - Study Eye	8.6 (± 9)	5.9 (± 6.8)	5.9 (± 6.8)	6.6 (± 7.3)
overall Visit 6 - Study Eye	9.4 (± 7.8)	8.4 (± 8.1)	8.2 (± 6.8)	8.8 (± 6.9)
overall Final Visit - Study Eye	8.7 (± 10.2)	7.7 (± 9.6)	9.8 (± 8.8)	10.8 (± 8.9)
overall Visit 2 - Non Study Eye	10.1 (± 8.1)	9.4 (± 6.2)	8.6 (± 8.7)	10.2 (± 9.1)
overall Visit 3- Non Study Eye	7.4 (± 9.4)	4.6 (± 5.5)	7.5 (± 8.1)	8.9 (± 8.5)
overall Visit 6 - Non Study Eye	11.4 (± 10.7)	10.8 (± 11.2)	9.4 (± 8.4)	10.8 (± 8.3)
overall Final Visit - Non Study Eye	8.8 (± 8.8)	7.6 (± 8.4)	9.6 (± 9.5)	11.3 (± 9.9)

Attachments (see zip file)	End Point/Schirmer's test type I.pdf

Statistical analyses

Statistical analysis title	Schirmer's test type I (without anaesthesia)

Statistical analysis description:

Values of Schirmer's test type I (i.e. tear wetting distance at 5 minutes) and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	34
Variability estimate	Standard deviation
Dispersion value	10.2

Primary: Treatment-emergent adverse events (TEAEs)

End point title	Treatment-emergent adverse events (TEAEs)

End point description:

AEs were coded by SOC and Preferred Term (PT), using the MedDRA.AEs were classified as pre-treatment AEs (PTAEs) and TEAEs according to the period of occurrence.TEAEs are summarised by dose and overall. The n° and % of patients with any TEAE and the n° of TEAEs are tabulated by SOC and PT, seriousness, relationship to treatment and severity. TEAEs are summarised in tables of frequency. The n° and % of patients with any TEAE, the n° of TEAEs, the n° and % of patients with any TEAE by severity, the n° of TEAEs by severity, the n° and % of patients with any TEAE related to study drug, the n° of TEAEs related to study drug are presented.Serious TEAEs are summarised by dose.The n° and % of patients with any serious TEAE, the n° of serious TEAEs, the n° and % of patients with any serious

TEAE,n° of serious TEAEs,n° and % of patients with any serious TEAE related to study drug and n° of serious TEAEs related to study drug are presented.

End point type	Primary

End point timeframe:

after the first dose of IMP.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of TEAEs				
n° of TEAEs	36	65		
n° of related TEAEs	11	4		
n° of patients with TEAEs	14	15		
n° of patients with related TEAEs	8	3		

Statistical analyses

Statistical analysis title	TEAEs

Statistical analysis description:

due to the low number patients it was possible to perform only a descriptive analisys calculation of the percentage of unrilated, related and overall TEAEs occured

Comparison groups	Group 2 v Group 1
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [1]
Method	not provided
Parameter estimate	not provided
Point estimate	0
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - not provided

Secondary: Visual analogue scale (VAS) for ocular tolerability (foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)

End point title	Visual analogue scale (VAS) for ocular tolerability (foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)

End point description:

A global ocular tolerability score was determined using a 100 mm VAS on which 0 meant no symptoms

and 100 meant the worst possible discomfort. This evaluation was to be performed before any ophthalmic assessment at each scheduled visit. Specific ocular symptoms to be measured with the VAS included:
foreign body sensation,
burning/stinging,
itching,
pain,
sticky feeling
blurred vision
photophobia
The patients evaluated their symptoms using the VAS giving the value they were feeling from none to an extreme value. The patients were expected to complete the evaluation in about 5 min.

End point type	Secondary
End point timeframe:	
visit 1, visit 2, visit 3, visit 6 and final visit	

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: 100 mm VAS				
arithmetic mean (standard deviation)				
overall visit 2 Foreign B.S. Study Eye	29.6 (± 26.5)	27.8 (± 27.1)	47.1 (± 28.6)	43.3 (± 24.1)
overall visit 3 Foreign B.S. Study Eye	22.8 (± 25.3)	18.5 (± 25.3)	28.4 (± 27.4)	27.7 (± 26.3)
overall visit 6 Foreign B.S. Study Eye	16.6 (± 24.7)	15.5 (± 24.8)	18.7 (± 19.5)	18.3 (± 20)
overall final visit Foreign B.S. Study Eye	17.4 (± 25.8)	16.1 (± 25.4)	18.4 (± 25.9)	12.8 (± 15)
overall visit 2 Foreign B.S. Non Study Eye	23 (± 23.3)	20.2 (± 21.5)	43.4 (± 28.7)	40.6 (± 25)
overall visit 3 Foreign B.S. Non Study Eye	19.5 (± 23.4)	13.7 (± 20.9)	34.5 (± 31.2)	33.2 (± 31.5)
overall visit 6 Foreign B.S. Non Study Eye	14.8 (± 21.1)	12.2 (± 17.4)	20 (± 23.1)	18 (± 20)
overall final visit Foreign B.S. Non Study Eye	14.5 (± 21.4)	12.7 (± 18.2)	20.4 (± 26.5)	15.9 (± 19.7)
overall visit 2 Burning/Stinging Study Eye	26.9 (± 24.8)	22.9 (± 25)	39.4 (± 28.6)	35.8 (± 25.8)
overall visit 3 Burning/Stinging Study Eye	22.4 (± 24.2)	17.9 (± 23.7)	33.1 (± 28.6)	27.6 (± 27.8)
overall visit 6 Burning/Stinging Study Eye	15.5 (± 24.7)	15.1 (± 24.3)	21.2 (± 23.4)	19.6 (± 22)
overall final visit Burning/Stinging Study Eye	18 (± 25.7)	17.2 (± 25.2)	16.9 (± 23.6)	10.6 (± 11.6)
overall visit 2 Burning/Stinging Non Study Eye	23.5 (± 21.6)	17.7 (± 18.6)	41.4 (± 29.7)	37.3 (± 26.6)
overall visit 3 Burning/Stinging Non Study Eye	20 (± 22.9)	13.5 (± 18.2)	27.5 (± 27.7)	24.9 (± 27.5)
overall visit 6 Burning/Stinging Non Study Eye	12.4 (± 19.1)	10.6 (± 16.7)	22.6 (± 24.3)	20.6 (± 22.3)
overall final visit Burning/Stinging Non Study Eye	15.2 (± 21.4)	14.1 (± 18.3)	20.7 (± 26.7)	13.5 (± 17.6)
overall visit 2 Itching Study Eye	28.7 (± 26.2)	23 (± 27.1)	40 (± 30)	36.6 (± 26.9)
overall visit 3 Itching Study Eye	19.6 (± 18.1)	15.6 (± 20.4)	29.9 (± 29.9)	26.8 (± 30)
overall visit 6 Itching Study Eye	12.7 (± 21)	14.4 (± 23.7)	19.1 (± 22.4)	18.8 (± 23.6)
overall final visit Itching Study Eye	17.4 (± 26.4)	17.5 (± 25.7)	18.8 (± 21.9)	11.1 (± 12.3)

overall visit 2 Itching Non Study Eye	20.5 (± 17.9)	16.3 (± 18.6)	39 (± 30.9)	35.7 (± 28.2)
overall visit 3 Itching Non Study Eye	21.1 (± 22.1)	13.9 (± 19)	29.8 (± 29.8)	25.5 (± 31.3)
overall visit 6 Itching Non Study Eye	9.5 (± 13.4)	10.6 (± 15.8)	18.2 (± 22.1)	15.9 (± 20.1)
overall final visit Itching Non Study Eye	14.7 (± 23.1)	14.5 (± 20.2)	19.4 (± 23.4)	13 (± 15.6)
overall visit 2 Pain Study Eye	21.5 (± 24.6)	20.3 (± 25.6)	27 (± 25)	23.4 (± 17.5)
overall visit 3 Pain Study Eye	25.3 (± 34.2)	24.4 (± 34.6)	25.4 (± 27.8)	22.9 (± 23.6)
overall visit 6 Pain Study Eye	16.3 (± 28.2)	15.7 (± 27.4)	16.1 (± 24.9)	14.3 (± 23.3)
overall final visit Pain Study Eye	15.8 (± 27)	16 (± 26.5)	12.6 (± 20.3)	7.6 (± 9.9)
overall visit 2 Pain Non Study Eye	13.3 (± 14.5)	11.1 (± 16.2)	27.3 (± 24.3)	23.2 (± 15.9)
overall visit 3 Pain Non Study Eye	21.1 (± 30.4)	18.7 (± 28.7)	29.9 (± 28.2)	26.9 (± 26.4)
overall visit 6 Pain Non Study Eye	9.6 (± 17.4)	7.6 (± 13.8)	17.9 (± 24.1)	16.6 (± 22.7)
overall final visit Pain Non Study Eye	12.7 (± 22.3)	11.9 (± 18.6)	14.4 (± 23.5)	9.2 (± 15.1)
overall visit 2 Sticky Feeling Study Eye	21 (± 22)	26 (± 24.3)	37.4 (± 30.9)	34.3 (± 29.5)
overall visit 3 Sticky Feeling Study Eye	18.5 (± 21.9)	19.3 (± 25.1)	21.9 (± 27.3)	22.3 (± 27.5)
overall visit 6 Sticky Feeling Study Eye	17.5 (± 28.9)	16.5 (± 25.7)	16.6 (± 26.4)	14.6 (± 24.5)
overall final visit Sticky Feeling Study Eye	17.1 (± 30.1)	17.1 (± 29.7)	16.2 (± 23.6)	11.2 (± 17.8)
overall visit 2 Sticky Feeling Non Study Eye	19.5 (± 21.7)	20.2 (± 20.8)	31.5 (± 30.5)	27.9 (± 28.4)
overall visit 3 Sticky Feeling Non Study Eye	16.5 (± 19.9)	13.9 (± 16.9)	22 (± 27.6)	22.1 (± 27.1)
overall visit 6 Sticky Feeling Non Study Eye	12.4 (± 23)	9.2 (± 13.6)	17.7 (± 26.9)	15.6 (± 25)
overall final visit Sticky Feeling Non Study Eye	15.8 (± 27.6)	14.9 (± 24.8)	16.4 (± 24.1)	11 (± 18.1)
overall visit 2 Blurred Vision Study Eye	34.7 (± 25.6)	32.7 (± 26.7)	47.5 (± 31.7)	45.1 (± 28.4)
overall visit 3 Blurred Vision Study Eye	28.8 (± 28.5)	24.3 (± 29.3)	37.3 (± 32.5)	34.8 (± 30.4)
overall visit 6 Blurred Vision Study Eye	17.7 (± 26.5)	16.4 (± 26.2)	25.7 (± 28)	19.9 (± 21)
overall final visit Blurred Vision Study Eye	19.3 (± 27.6)	19.6 (± 28.3)	26.1 (± 27.9)	20.5 (± 21.3)
overall visit 2 Blurred Vision Non Study Eye	30.3 (± 21.5)	26.9 (± 22.2)	43.5 (± 33.5)	40.3 (± 30.6)
overall visit 3 Blurred Vision Non Study Eye	25.9 (± 25.9)	22 (± 25.5)	34.5 (± 32.7)	30.9 (± 29.5)
overall visit 6 Blurred Vision Non Study Eye	16 (± 20.7)	14.6 (± 18.1)	27.3 (± 28.8)	22.3 (± 23.9)
overall final visit Blurred Vision Non Study Eye	17 (± 24.9)	16.9 (± 23.9)	24 (± 28.1)	18.4 (± 21.7)
overall visit 2 Photophobia Study Eye	38.9 (± 30.6)	40.1 (± 30.1)	53.1 (± 32.5)	56.4 (± 29.7)
overall visit 3 Photophobia Study Eye	32.9 (± 30.5)	31.9 (± 30.6)	37.3 (± 31.7)	37.4 (± 33.4)
overall visit 6 Photophobia Study Eye	28.4 (± 31.2)	30.6 (± 30.3)	29.8 (± 34.8)	23.8 (± 31.3)
overall final visit Photophobia Study Eye	27.7 (± 32.3)	29.9 (± 31.5)	25.1 (± 26.8)	23.7 (± 27.9)
overall visit 2 Photophobia Non Study Eye	37 (± 28.2)	35.1 (± 27.7)	50.1 (± 30.2)	52.8 (± 26.7)
overall visit 3 Photophobia Non Study Eye	30.3 (± 28)	29.4 (± 27)	32.2 (± 29.7)	31.4 (± 30.8)
overall visit 6 Photophobia Non Study Eye	21.9 (± 27.8)	21.9 (± 25.8)	31 (± 35.5)	25.8 (± 33)
overall final visit Photophobia Non Study Eye	24.2 (± 29.1)	25.7 (± 26.6)	24.1 (± 24.4)	22.1 (± 24.7)

Attachments (see zip file)	End Point/Visual analogue scale (VAS) for ocular tolerability.pdf

Statistical analyses

Statistical analysis title	Visual analogue scale (VAS)for ocular tolerability

Statistical analysis description:

VAS values for ocular tolerability symptoms and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	17.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	84
Variability estimate	Standard deviation
Dispersion value	25.8

Secondary: Slit lamp examination (Eyelid - meibomian glands, eyelid – erythema, eyelid - oedema lashes, conjunctiva erythema, lens, iris, anterior chamber)

End point title	Slit lamp examination (Eyelid - meibomian glands, eyelid – erythema, eyelid - oedema lashes, conjunctiva erythema, lens, iris, anterior chamber)

End point description:

The slit lamp examination was performed before the instillation of any dilating or anaesthetic eye drops or the fluorescein agent (Fluorescein Minims, Fluorescein sodium 2%).
The patient was sitting at the slit lamp while being examined. Grading of the eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: SLE (Slit lamp examination scale)				
arithmetic mean (standard deviation)				

overall-Eyelid-Meibomian glands-visit 2 Study Eye	1.3 (± 0.8)	1.1 (± 0.8)	0.5 (± 0.6)	0.4 (± 0.5)
overall-Eyelid-Meibomian glands-visit 3 Study Eye	1.1 (± 0.7)	0.9 (± 0.5)	0.3 (± 0.6)	0.3 (± 0.4)
overall-Eyelid-Meibomian glands-visit 6 Study Eye	0.6 (± 0.8)	0.4 (± 0.5)	0.4 (± 0.5)	0.4 (± 0.5)
overall-Eyelid-Meibomian glands-final v- Study Eye	0.8 (± 0.6)	0.8 (± 0.6)	0.4 (± 0.5)	0.4 (± 0.5)
overall-Eyelid - Erythema - visit 2 - Study Eye	0.8 (± 0.8)	0.8 (± 0.7)	0.3 (± 0.7)	0.3 (± 0.6)
overall-Eyelid - Erythema - visit 3 - Study Eye	0.6 (± 0.6)	0.5 (± 0.5)	0.4 (± 0.7)	0.3 (± 0.7)
overall-Eyelid - Erythema - visit 6 - Study Eye	0.2 (± 0.4)	0.1 (± 0.3)	0.4 (± 0.7)	0.4 (± 0.6)
overall-Eyelid - Erythema - final visit - Study Eye	0.2 (± 0.4)	0.1 (± 0.3)	0.3 (± 0.4)	0.3 (± 0.4)
overall-Eyelid Oedema - visit 2 - Study Eye	0.6 (± 0.6)	0.6 (± 0.6)	0.3 (± 0.6)	0.3 (± 0.6)
overall-Eyelid Oedema - visit 3 - Study Eye	0.2 (± 0.4)	0.2 (± 0.4)	0.4 (± 0.7)	0.4 (± 0.7)
overall-Eyelid Oedema - visit 6 - Study Eye	0.1 (± 0.2)	0.1 (± 0.3)	0.4 (± 0.7)	0.4 (± 0.6)
overall-Eyelid Oedema - final visit - Study Eye	0.1 (± 0.2)	0.1 (± 0.3)	0.3 (± 0.6)	0.3 (± 0.6)
overall - Lashes - visit 2- Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes - visit 3 - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes - visit 6 - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes - final visit - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Conju.Erythema- visit 2 - Study Eye	1.4 (± 0.5)	1.1 (± 0.4)	1.3 (± 0.6)	1.3 (± 0.6)
overall- Conju.Erythema- visit 3 - Study Eye	1.2 (± 0.6)	1.1 (± 0.7)	1 (± 0.3)	1 (± 0.4)
overall- Conju.Erythema- visit 6 - Study Eye	1.1 (± 0.5)	1 (± 0.4)	1 (± 0.6)	1 (± 0.5)
overall- Conju.Erythema- final visit - Study Eye	1.1 (± 0.6)	1.1 (± 0.5)	1 (± 0.5)	0.9 (± 0.4)
overall-Conju.Oedema- visit 2 - Study Eye	1.1 (± 0.9)	0.7 (± 0.5)	0.6 (± 0.7)	0.6 (± 0.6)
overall-Conju.Oedema- visit 3 - Study Eye	0.8 (± 0.6)	0.8 (± 0.6)	0.5 (± 0.5)	0.6 (± 0.5)
overall-Conju.Oedema- visit 6 - Study Eye	0.5 (± 0.5)	0.5 (± 0.5)	0.5 (± 0.7)	0.5 (± 0.7)
overall-Conju.Oedema- final visit - Study Eye	0.9 (± 0.6)	0.7 (± 0.5)	0.3 (± 0.7)	0.3 (± 0.7)
overall- Lens - visit 2- Study Eye	0.4 (± 0.5)	0.3 (± 0.5)	0.4 (± 0.6)	0.4 (± 0.7)
overall- Lens - visit 3 - Study Eye	0.4 (± 0.5)	0.2 (± 0.4)	0.4 (± 0.6)	0.4 (± 0.7)
overall- Lens - visit 6 - Study Eye	0.3 (± 0.5)	0.2 (± 0.4)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Lens - final visit - Study Eye	0.3 (± 0.5)	0.2 (± 0.4)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Iris - visit 2- Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - visit 3- Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - visit 6- Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - final visit - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- visit 2- Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- visit 3 - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- visit 6 - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- final visit - Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

overall-Eyelid-Meib. glands-visit 2-Non Study Eye	1.1 (± 0.7)	0.9 (± 0.6)	0.5 (± 0.7)	0.5 (± 0.6)
overall-Eyelid-Meib. glands-visit 3-Non Study Eye	1 (± 0.7)	0.8 (± 0.6)	0.5 (± 0.7)	0.5 (± 0.6)
overall-Eyelid-Meib. glands-visit 6-Non Study Eye	0.7 (± 0.7)	0.6 (± 0.5)	0.3 (± 0.5)	0.3 (± 0.5)
overall-EyelidMeibglands-final visit Non Study Eye	0.7 (± 0.7)	0.6 (± 0.6)	0.4 (± 0.5)	0.4 (± 0.5)
overall-Eyelid-Erythema- visit 2-Non Study Eye	0.8 (± 0.7)	0.7 (± 0.6)	0.4 (± 0.8)	0.3 (± 0.8)
overall-Eyelid-Erythema- visit 3-Non Study Eye	0.6 (± 0.6)	0.5 (± 0.5)	0.4 (± 0.8)	0.3 (± 0.8)
overall-Eyelid-Erythema- visit 6-Non Study Eye	0.2 (± 0.4)	0.1 (± 0.3)	0.3 (± 0.6)	0.3 (± 0.4)
overall-Eyelid-Erythema-final visit-Non Study Eye	0.2 (± 0.4)	0.1 (± 0.3)	0.2 (± 0.4)	0.2 (± 0.4)
overall-Eyelid Oedema-visit 2-Non Study Eye	0.5 (± 0.5)	0.5 (± 0.5)	0.3 (± 0.6)	0.3 (± 0.6)
overall-Eyelid Oedema-visit 3-Non Study Eye	0.2 (± 0.4)	0.1 (± 0.4)	0.4 (± 0.8)	0.4 (± 0.9)
overall-Eyelid Oedema-visit 6-Non Study Eye	0.1 (± 0.2)	0.1 (± 0.3)	0.4 (± 0.7)	0.3 (± 0.6)
overall-Eyelid Oedema-final visit-Non Study Eye	0.1 (± 0.2)	0.1 (± 0.3)	0.2 (± 0.5)	0.2 (± 0.5)
overall - Lashes - visit 2- Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes - visit 3 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes - visit 6 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall - Lashes -final visit- Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Conju.Erythe.- visit 2-Non Study Eye	1.4 (± 0.5)	1.2 (± 0.4)	1.2 (± 0.5)	1.2 (± 0.5)
overall- Conju.Erythe.- visit 3 -Non Study Eye	1.1 (± 0.6)	1 (± 0.6)	1.1 (± 0.4)	1.1 (± 0.5)
overall- Conju.Erythe.- visit 6 -Non Study Eye	1 (± 0.5)	1 (± 0.4)	0.9 (± 0.6)	0.9 (± 0.5)
overall- Conju.Erythe.- final visit-Non Study Eye	0.9 (± 0.6)	1 (± 0.4)	1 (± 0.5)	0.9 (± 0.4)
overall-Conju.Oedema-visit 2-Non Study Eye	1.1 (± 0.8)	0.7 (± 0.5)	0.7 (± 0.7)	0.7 (± 0.6)
overall-Conju.Oedema-visit 3 -Non Study Eye	0.8 (± 0.4)	0.8 (± 0.4)	0.6 (± 0.6)	0.6 (± 0.6)
overall-Conju.Oedema-visit 6 -Non Study Eye	0.4 (± 0.5)	0.4 (± 0.5)	0.5 (± 0.7)	0.5 (± 0.7)
overall-Conju.Oedema-final visit-Non Study Eye	0.7 (± 0.6)	0.6 (± 0.5)	0.3 (± 0.7)	0.3 (± 0.7)
overall- Lens - visit 2- Non Study Eye	0.4 (± 0.5)	0.3 (± 0.5)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Lens - visit 3- Non Study Eye	0.4 (± 0.5)	0.2 (± 0.4)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Lens - visit 6 - Non Study Eye	0.3 (± 0.5)	0.2 (± 0.4)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Lens - final visit - Non Study Eye	0.3 (± 0.5)	0.2 (± 0.4)	0.3 (± 0.5)	0.3 (± 0.5)
overall- Iris - visit 2- Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - visit 3 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - visit 6 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Iris - final visit - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- visit 2- Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.- visit 3 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

overall- Ant.Cham.Infl.- visit 6 - Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall- Ant.Cham.Infl.-final visit -Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Attachments (see zip file)	End Point/Slit lamp examination.pdf

Statistical analyses

Statistical analysis title	Slit lamp examination

Statistical analysis description:

Slit lamp examination scores and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	2
Variability estimate	Standard deviation
Dispersion value	0.6

Secondary: Schirmer test type II (with anaesthesia)

End point title	Schirmer test type II (with anaesthesia)

End point description:

This test was performed to measure basal aqueous tear secretion following the instillation of a preservative-free anaesthetic eye drop (Oxybuprocaine Chlorhydrate 0.4%). Both eyes could be tested at the same time. Schirmer plus® strips (Gecis, France) were used.
This test was conducted in a dimly lit room. While the patient looked upwards, the lower lid was drawn gently downwards and temporarily. The rounded bent end of a sterile strip was inserted into the lower conjunctival sac over the temporal one-third of the lower eyelid margin. The test was done without touching directly the Schirmer test strip with the fingers to avoid contamination of skin oils. The patients were instructed to close their eyes gently.
After 5 minutes, the Schirmer test strip was removed and the length of the tear absorption on the strip was measured (mm/5 min).

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: 0 mm/5 minutes				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	11.3 (± 8.7)	10.6 (± 7.5)	9.3 (± 7.6)	10.1 (± 8.1)
overall visit 3 Study Eye	14.9 (± 10.6)	15 (± 10.5)	8.9 (± 6.9)	10.1 (± 7.2)
overall visit 6 Study Eye	17 (± 9.2)	15.8 (± 8.9)	13.2 (± 11)	15 (± 11)
overall final visit Study Eye	15.4 (± 9.6)	14.5 (± 8.7)	13.7 (± 8.5)	15.1 (± 8.7)
overall visit 2 Non Study Eye	13.5 (± 8.7)	13.8 (± 7.6)	9.4 (± 7.1)	10.6 (± 7.5)
overall visit 3 Non Study Eye	14 (± 10.4)	14.7 (± 11)	10.3 (± 6.1)	11.6 (± 6.2)
overall visit 6 Non Study Eye	18.1 (± 9.4)	16.6 (± 9.77)	13.5 (± 10.4)	15.6 (± 9.9)
overall final visit Non Study Eye	15 (± 8.2)	14.2 (± 7)	12.5 (± 9.3)	14.8 (± 8.9)

Attachments (see zip file)	End Point/Schirmer's test type II.pdf

Statistical analyses

Statistical analysis title	Schirmer test type II (with anaesthesia)

Statistical analysis description:

Values of Schirmer's test type II (i.e. tear wetting distance at 5 minutes) and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	8.7
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	2
upper limit	30
Variability estimate	Standard deviation
Dispersion value	9.6

Secondary: Tear film break-up time (TFBUT)

End point title	Tear film break-up time (TFBUT)

End point description:

Patients with a TFBUT test ≤10 in the worse eye (study eye) at the screening visit were eligible for enrolment.
TFBUT was measured by determining the time to tear break-up. The TFBUT was performed after instillation of 5 µl of 2% preservative-free sodium fluorescein solution (using Fluorescein Minims, Fluorescein sodium 2% Chauvin Pharmaceuticals Ltd,106 London Road, Kingston-upon-Thames; Surrey KT2 6TN, UK, with UK marketing authorization PL 0033/5008R) into the inferior conjunctival cul-de-sac of each eye. The patient was instructed to blink several times to thoroughly mix the fluorescein with the tear film. In order to achieve maximum fluorescence, the examiner waited approximately 30 seconds after instillation before evaluating TFBUT.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	13	16
Units: second				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	4 (± 1.8)	4.1 (± 2)	2.3 (± 2.1)	2.6 (± 2.2)
overall visit 3 Study Eye	4.9 (± 2.2)	5.1 (± 2.2)	2.7 (± 1.7)	2.7 (± 1.7)
overall visit 6 Study Eye	6 (± 2.5)	5.9 (± 2.4)	2.5 (± 1.3)	2.6 (± 1.3)
overall final visit Study Eye	5.6 (± 2.4)	5.3 (± 1.9)	2.7 (± 2.1)	2.9 (± 2.1)
overall visit 2 Non Study Eye	4.5 (± 2.2)	4.4 (± 2.4)	2.9 (± 1.9)	2.9 (± 1.8)
overall visit 3 Non Study Eye	5.2 (± 2.4)	5.6 (± 2.2)	3 (± 1.6)	3.1 (± 1.7)
overall visit 6 Non Study Eye	6 (± 2.6)	6 (± 2.9)	2.6 (± 1.2)	2.8 (± 1.1)
overall final visit Non Study Eye	5.7 (± 2.5)	5.9 (± 3)	2.6 (± 1.6)	2.8 (± 1.6)

Attachments (see zip file)	End Point/Tear film break-up time.pdf

Statistical analyses

Statistical analysis title	Tear film break-up time (TFBUT)

Statistical analysis description:

Values of tear film break-up time and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment

	in dry eye gruppo2)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	2
upper limit	12
Variability estimate	Standard deviation
Dispersion value	2.4

Secondary: Corneal fluorescein staining

End point title	Corneal fluorescein staining

End point description:

Corneal fluorescein staining scores, total corneal staining scores and their changes from baseline (screening visit assessment) are listed and summarised using classic descriptive statistics by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit. Corneal fluorescein staining scores and total corneal staining scores were compared within each dose group, disease severity at screening, evaluation visit and eye (study eye and non study eye) versus their baseline values by a two-sided Wilcoxon signed-rank test with a nominal α level of 0.05.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: ranking test				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	4.9 (± 2.8)	4.6 (± 3.1)	5.6 (± 3.7)	5.1 (± 3.2)
overall visit 3 Study Eye	3.3 (± 2.6)	3.1 (± 2.9)	4.8 (± 3.8)	4.2 (± 3.3)
overall visit 6 Study Eye	2.1 (± 2.2)	1.8 (± 2.2)	4.1 (± 3.6)	3.8 (± 3.4)
overall final visit Study Eye	2.4 (± 2.2)	2.6 (± 2.5)	4 (± 3)	3.7 (± 2.8)
overall visit 2 Non Study Eye	4.4 (± 3.1)	3.7 (± 3.2)	4.5 (± 3.1)	3.9 (± 2)
overall visit 3 Non Study Eye	3.1 (± 2.3)	2.7 (± 2.4)	4.1 (± 3.8)	3.4 (± 3.1)
overall visit 6 Non Study Eye	1.9 (± 2.4)	1.7 (± 2.3)	3.7 (± 3.3)	3.1 (± 2.3)
overall final visit Non Study Eye	2.2 (± 1.9)	2.1 (± 2)	3.8 (± 2.9)	3.5 (± 2.8)

Statistical analyses

Statistical analysis title	Corneal fluorescein staining
Statistical analysis description:	
Corneal fluorescein staining scores, total corneal staining score and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.	
Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	7
Variability estimate	Standard deviation
Dispersion value	2.2

Secondary: Corneal sensitivity (Cochet-Bonnet aesthesiometry)

End point title	Corneal sensitivity (Cochet-Bonnet aesthesiometry)
End point description:	
For the assessment of corneal sensation the Luneau Cochet-Bonnet aesthesiometer (Western Ophthalmics Corporation©) was used. Corneal sensation was measured in both eyes in each of the four quadrants of the cornea using the Cochet Bonnet aesthesiometer before the instillation of any dilating or anesthetic eye drops.	
End point type	Secondary
End point timeframe:	
visit 1, visit 2, visit 3, visit 6 and final visit	

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: cm				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	5.65 (± 0.54)	5.64 (± 0.6)	5.63 (± 0.99)	5.91 (± 0.27)
overall visit 3 Study Eye	5.63 (± 0.72)	5.57 (± 0.83)	5.8 (± 0.44)	5.91 (± 0.38)
overall visit 6 Study Eye	5.93 (± 0.18)	5.89 (± 0.21)	5.79 (± 0.61)	5.75 (± 0.66)
overall final visit Study Eye	5.88 (± 0.39)	5.82 (± 0.46)	5.93 (± 0.18)	5.91 (± 0.2)
overall visit 2 Non Study Eye	5.85 (± 0.37)	5.86 (± 0.36)	5.73 (± 0.7)	5.94 (± 0.17)
overall visit 3 Non Study Eye	5.83 (± 0.34)	5.79 (± 0.38)	5.9 (± 0.31)	6 (± 0)
overall visit 6 Non Study Eye	5.93 (± 0.18)	5.89 (± 0.21)	5.89 (± 0.21)	5.91 (± 0.2)
overall final visit Non Study Eye	5.9 (± 0.31)	5.86 (± 0.36)	5.85 (± 0.29)	5.91 (± 0.2)

Statistical analyses

Statistical analysis title	Corneal sensitivity (Cochet-Bonnet aesthesiometry)

Statistical analysis description:

Values of corneal sensitivity (i.e. the length of the filament in cm at which the patient corneal sensation was observed) and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	5.88
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	4.5
upper limit	6
Variability estimate	Standard deviation
Dispersion value	0.39

Secondary: Intraocular pressure (IOP)

End point title	Intraocular pressure (IOP)

End point description:

IOP was performed using either Goldmann applanation tonometry or a handheld applanation tonometer

(e.g. Tonopen) after the instillation of a topical anaesthetic. IOP was measured in both eyes after completion of all other slit lamp examinations to avoid potential interference with the other evaluations. The patient's position was adjusted until the patient's head was firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes were tested, with the right eye preceding the left eye. The same equipment was used throughout the study. IOP for each eye in mmHg was recorded in the CRF.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: mmHg				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	15 (± 1.6)	14.7 (± 1.4)	12.9 (± 2.4)	12.9 (± 2.3)
overall visit 3 Study Eye	14.1 (± 1.6)	14 (± 1.6)	13.2 (± 2.9)	12.4 (± 2.4)
overall visit 6 Study Eye	14.4 (± 1.9)	14.4 (± 1.7)	14.1 (± 2.4)	13.8 (± 2.2)
overall final visit Study Eye	14.2 (± 2.7)	14.4 (± 3.1)	13.6 (± 2.5)	13.6 (± 2.2)
overall visit 2 Non Study Eye	14.9 (± 1.6)	14.5 (± 1.4)	13.2 (± 2.2)	12.9 (± 2.3)
overall visit 3 Non Study Eye	13.9 (± 2)	13.8 (± 1.9)	12.8 (± 2.4)	12.5 (± 1.8)
overall visit 6 Non Study Eye	13.9 (± 2)	13.6 (± 1.9)	13.9 (± 1.8)	13.6 (± 1.6)
overall final visit Non Study Eye	14 (± 2.7)	14.1 (± 2.6)	13.7 (± 2.4)	13.7 (± 2.2)

Statistical analyses

Statistical analysis title	Intraocular pressure (IOP)

Statistical analysis description:

Values of intraocular pressure and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	14.2

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	8
upper limit	18
Variability estimate	Standard deviation
Dispersion value	2.7

Secondary: Visual acuity (early treatment diabetic retinopathy study [ETDRS] chart)

End point title	Visual acuity (early treatment diabetic retinopathy study [ETDRS] chart)

End point description:

Refraction and visual acuity measurements were performed for all patients by trained vision examiners only. The name and certification number of the vision examiner were documented in the patient's visual acuity (VA) worksheet (provided by the Sponsor) at each visit.
Refraction was measured prior to visual acuity testing to obtain best-corrected vision as described below. Best-corrected visual acuity was measured at all visits using standard charts, lighting, and procedures. Best correction was determined by careful refraction at that visit according to the standard protocol for refraction as described below. The refraction equipment required included:
Retroilluminated Light box and ETDRS 4 meter distance acuity chart set
Trial lens frames
Trial lens set with plus or minus cylinder lenses
Jackson cross-cylinders of 0.25, 0.50, and 1.00 diopters
Pinhole occluder
Tissues or eye pads and tape
A 1 meter rigid measuring stick
Visual acuity chart 1 was used for test

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: cm				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	86.1 (± 5.1)	86.6 (± 5.9)	76.2 (± 20.9)	78.5 (± 13.5)
overall visit 3 Study Eye	85.9 (± 5.1)	85.8 (± 6.1)	78 (± 19.4)	80 (± 14.4)
overall visit 6 Study Eye	86.7 (± 4.4)	87.3 (± 5.1)	78.9 (± 15.4)	79.9 (± 14.5)
overall final visit Study Eye	86.6 (± 3.7)	87 (± 4.2)	81.3 (± 13.3)	82.8 (± 11.2)
overall visit 2 Non Study Eye	87.3 (± 3.9)	87.9 (± 4.3)	80.9 (± 10.7)	81.9 (± 9.8)
overall visit 3 Non Study Eye	87.1 (± 4.1)	86.8 (± 4.6)	81.2 (± 11.6)	81.7 (± 10.3)
overall visit 6 Non Study Eye	87 (± 4.8)	87.4 (± 5.5)	81 (± 11.5)	82.2 (± 10)
overall final visit Non Study Eye	87 (± 4)	87.1 (± 4.4)	82.3 (± 10.4)	81.9 (± 1.3)

Attachments (see zip file)	End Point/Visual acuity.pdf

Statistical analyses

Statistical analysis title	Visual acuity (early treatment diabetic retinopath

Statistical analysis description:

Values of visual acuity and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	86.6
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	82
upper limit	95
Variability estimate	Standard deviation
Dispersion value	3.7

Secondary: Fundus ophthalmoscopy

End point title	Fundus ophthalmoscopy

End point description:

The fundus examination included ophthalmoscopic assessments of vitreous, macula, retina and optic nerve head for both eyes. For the screening examination of the fundus oculi, the pupils were dilated. For examination of the fundus oculi, dilation was only required in the event of an assessment of an AE.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: grades				
arithmetic mean (standard deviation)				
overall Vitreous - visit 2 Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - visit 3 Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)

overall Vitreous - visit 6 Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - final visit Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - visit 2 Non Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - visit 3 Non Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - visit 6 Non Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall Vitreous - final visit Non Study Eye	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 2 Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 3 Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 6 Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - final visit Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 2 Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 3 Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. - visit 6 Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
overall M.R. and O.N.H. -final visit Non Study Eye	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Attachments (see zip file)	End Point/Fundus ophthalmoscopy.pdf

Statistical analyses

Statistical analysis title	Fundus ophthalmoscopy

Statistical analysis description:

Fundus ophthalmoscopy scores and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	1
Variability estimate	Standard deviation
Dispersion value	0.2

Secondary: Tear film osmolarity

End point title	Tear film osmolarity

End point description:

Tear film osmolarity as a marker of tear film solute content was performed with a TearLab Osmolarity System.The concentration of the tears was assessed in both eyes before the instillation of any dilating or anesthetic drops.To perform the test, the patient was sitting with head tilted back and eyes looking upward towards the ceiling. One hand was placed on the patient's face for stabilisation.The eyelid was not moved away from the eye as pulling the eyelid down would have broken the tear lake and hindered the tear film collection.The handheld TearLab Osmolarity Pen was placed close to the eye just above the outer 1/3 of the lower eyelid and gently lower allowing the bottom of the tip to come into contact with the lower eyelid and the line of moisture along the inner eyelid margin.While avoiding contact with the bulbar conjunctiva, the Pen tip was pressed down lightly on the eyelid to collect the tears.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: mOsm/L				
arithmetic mean (standard deviation)				
overall visit 2 Study Eye	304.6 (± 9.1)	303.4 (± 9.5)	313.2 (± 16.8)	314.6 (± 18.2)
overall visit 3 Study Eye	309.6 (± 11.9)	308.3 (± 13.4)	314.4 (± 19.2)	313.2 (± 21)
overall visit 6 Study Eye	308.2 (± 12.3)	305.9 (± 12)	312.5 (± 12.3)	313.6 (± 13.1)
overall final visit Study Eye	308.8 (± 9.8)	308.1 (± 11.1)	318 (± 18.3)	315.3 (± 17.9)
overall visit 2 Non Study Eye	307.1 (± 20.5)	302.9 (± 14)	319.9 (± 20.9)	321.3 (± 22.3)
overall visit 3 Non Study Eye	304.4 (± 11.3)	303 (± 12.1)	314.1 (± 19)	314.6 (± 21.5)
overall visit 6 Non Study Eye	307 (± 12.9)	303.7 (± 8)	307.6 (± 12.7)	307.8 (± 8.2)
overall final visit Non Study Eye	311.7 (± 10.1)	311.3 (± 11.4)	313.7 (± 20.3)	314 (± 22.6)

Attachments (see zip file)	End Point/Tear film osmolarity.pdf

Statistical analyses

Statistical analysis title	Tear film osmolarity

Statistical analysis description:

Values of tear film osmolarity and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening, eye (study eye and non study eye) and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment

	in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	308.8
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	291
upper limit	326
Variability estimate	Standard deviation
Dispersion value	9.8

Secondary: Conjunctival impression cytology for goblet cells' count

End point title	Conjunctival impression cytology for goblet cells' count

End point description:

Values of conjunctival impression cytology for goblet cells' count and their changes from baseline (screening visit assessment), mean±SD of 3 consecutive optic fields and mean±SD of changes from baseline of 3 consecutive optic fields for each impression cytology sample are listed. Mean of 3 consecutive optic fields and mean of changes from baseline of 3 consecutive optic fields for each impression cytology sample are summarised using classic descriptive statistics by dose group, disease severity at ascreening and evaluation visit. Values of conjunctival impression cytology for goblet cells' count were compared within each dose group, disease severity at screening and evaluation visit versus their baseline values by a two-sided Wilcoxon signed-rank test with a nominal α level of 0.05.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: α level				
arithmetic mean (standard deviation)				
overall visit 2 Temporal B.C.	5.04 (± 5.63)	5.43 (± 5.99)	1.62 (± 1.64)	1.69 (± 1.76)
overall visit 3 Temporal B.C.	4.17 (± 4.59)	4.05 (± 5.1)	1.47 (± 1.86)	1.71 (± 1.94)
overall visit 6 Temporal B.C.	6.35 (± 10.57)	4.94 (± 7.71)	2.15 (± 3.05)	2.51 (± 3.22)
overall final visit Temporal B.C.	3.9 (± 4.95)	2.75 (± 4.03)	1.82 (± 2.42)	1.9 (± 2.41)
overall visit 2 Nasal B.C.	3.92 (± 3.44)	3.39 (± 3.44)	1.5 (± 2.1)	1.81 (± 2.24)
overall visit 3 Nasal B.C.	5.82 (± 11.04)	2.33 (± 3.67)	2.93 (± 4.36)	3.47 (± 4.61)
overall visit 6 Nasal B.C.	5.18 (± 4.84)	5.09 (± 5.08)	1.53 (± 1.81)	1.67 (± 1.89)
overall final visit Nasal B.C.	5.97 (± 9.49)	4.9 (± 8.18)	2.82 (± 3.17)	3.33 (± 3.27)
overall visit 2 Inferior B.C.	3.61 (± 3.89)	4.44 (± 4.37)	1.23 (± 1.49)	1.4 (± 1.61)

overall visit 3 Inferior B.C.	5.63 (± 8.38)	2.33 (± 3.41)	1.32 (± 2.34)	1.54 (± 2.49)
overall visit 6 Inferior B.C.	2.88 (± 3.46)	2.15 (± 1.64)	1.05 (± 1.48)	1.23 (± 1.55)
overall final visit Inferior B.C.	5.26 (± 5.88)	4.72 (± 7.61)	2.33 (± 2.45)	2.6 (± 2.64)
overall visit 2 Superior B.C.	5.77 (± 9.97)	7.52 (± 11.17)	1.88 (± 2.58)	2.13 (± 2.81)
overall visit 3 Superior B.C.	5.7 (± 7.62)	4.19 (± 7.15)	1.58 (± 2.17)	1.96 (± 2.31)
overall visit 6 Superior B.C.	3.96 (± 4.87)	2.77 (± 3.83)	1.57 (± 1.87)	1.6 (± 1.93)
overall final visit Superior B.C.	5.98 (± 9.67)	4.81 (± 6.75)	2.2 (± 1.95)	2.56 (± 1.93)

Attachments (see zip file)	End Point/Conjunctival impression cytology for goblet cells'

Statistical analyses

Statistical analysis title	Conjunctival impression cytology for goblet cells'

Statistical analysis description:

Values of conjunctival impression cytology for goblet cells' count, their changes from baseline screening visit assessment),mean ±SD of 3 consecutive optic fields and mean ±SD of changes from baseline of 3 consecutive optic fields for each impression cytology sample
will be listed.Mean of 3 consecutive optic fields and mean of changes from baseline of 3 consecutive optic fields for each impression cytology sample will be summarised using classic descriptive statistics (i.e.arithmetic mean,SD)

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	14.3
Variability estimate	Standard deviation
Dispersion value	4.95

Secondary: Frequency of artificial tears use

End point title	Frequency of artificial tears use

End point description:

Frequencies of artificial tears use and their changes from baseline (screening visit assessment) are listed and summarised using classic descriptive statistics by dose group, disease severity at screening and evaluation visit. Artificial tears accountability is listed. The average frequency of artificial tear use during the study in the intervals Day 1 - Day 8, Day 9 - Day 29 and Day 30 - Day 56 is listed and summarised using classic descriptive statistics by dose group. The average use for each subject was calculated as the total number of drops used in each period divided by the actual period duration. Data were stratified according to the illness severity level.

End point type	Secondary

End point timeframe:

visit 1, visit 2, visit 3, visit 6 and final visit

End point values	FAS (symptoms assessment in dry eye,gruppo 1)	PP (Symptom assessment in dry eye gruppo 1)	FAS (Symptom assessment in dry eye gruppo 2)	PP (Symptom assessment in dry eye gruppo2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	14	20	16
Units: number of drops per day period				
Day 1 (00:00) - Day 8 (23:59)	10	7	12	9
Day 9 (00:00) - Day 29 (23:59)	10	8	13	9
Day 30 (00:00) - Day 56 (23:59)	11	9	12	9

Attachments (see zip file)	End Point/Frequency of artificial tears use.pdf

Statistical analyses

Statistical analysis title	Frequency of artificial tears use during the study

Statistical analysis description:

Frequencies of artificial tears use during the study and their changes from baseline (screening visit assessment) will be listed and summarised using classic descriptive statistics (i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values) by dose group, disease severity at screening and evaluation visit.

Comparison groups	FAS (symptoms assessment in dry eye,gruppo 1) v PP (Symptom assessment in dry eye gruppo 1) v FAS (Symptom assessment in dry eye gruppo 2) v PP (Symptom assessment in dry eye gruppo2)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.04
upper limit	7.85
Variability estimate	Standard deviation
Dispersion value	2.961

Secondary: Vital signs (blood pressure; BP, pulse rate; PR), body weight (BW), physical examinations.

End point title	Vital signs (blood pressure; BP, pulse rate; PR), body weight

	(BW), physical examinations.

End point description:

Values of vital signs, their changes from baseline (screening visit assessment) and, only for visits 2 and 3 post-dose assessments, their changes from pre-dose are listed. A table of all abnormal values of vital signs is presented and values of vital signs, their changes from baseline and, only for visits 2 and 3 post-dose assessments, their changes from pre-dose are summarised using classic descriptive statistics by dose group, evaluation visit and evaluation time point.

End point type	Secondary

End point timeframe:

Visit 1, Visit 2, visit 3, visit 6 and final dose

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic B. P. - Screening - Day -15/1	126.2 (± 15.1)	123.1 (± 18)		
Systolic B. P. - Visit 2 - Day 1 - Pre-dose	125.3 (± 11.9)	126.5 (± 13.3)		
Systolic B. P. - Visit 2 - Day 1 - Post-dose	118.4 (± 12.5)	123.3 (± 15.3)		
Systolic B. P. - Visit 3 - Day 8±1 - Pre-dose	123.6 (± 12)	120.1 (± 14.4)		
Systolic B. P. - Visit 3 - Day 8±1 - Post-dose	122 (± 13.6)	123.9 (± 14.6)		
Systolic B. P. - Visit 6 - Day 29±1	124.5 (± 14.4)	120.1 (± 10.6)		
Systolic B. P. - Final Visit - Day 56±4/ETV	122 (± 12)	125 (± 15.3)		
Diastolic B. P. - Screening - Day -15/-1	78.5 (± 8.5)	75.7 (± 10)		
Diastolic B. P. - Visit 2 - Day 1 - Pre-dose	76.9 (± 9.4)	77.5 (± 10.4)		
Diastolic B. P. - Visit 2 - Day 1 - Post-dose	75.6 (± 8.4)	76 (± 10.8)		
Diastolic B. P. - Visit 3 - Day 8±1 - Pre-dose	76.6 (± 11.8)	74 (± 9.8)		
Diastolic B. P. - Visit 3 - Day 8±1 - Post-dose	74.9 (± 9.9)	76.1 (± 9.8)		
Diastolic B. P. - Visit 6 - Day 29±1	75.1 (± 8.8)	74.3 (± 10.1)		
Diastolic B. P. - Final Visit - Day 56±4/ETV	76.7 (± 7.4)	75.8 (± 10.9)		

Attachments (see zip file)	End Point/Vital signs.pdf

Statistical analyses

Statistical analysis title	Vital signs (blood pressure)
Comparison groups	Group 1 v Group 2

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	122
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	100
upper limit	141
Variability estimate	Standard deviation
Dispersion value	12

Secondary: Vital signs (pulse rate)

End point title	Vital signs (pulse rate)
End point description:	
End point type	Secondary
End point timeframe:	
Vital signs (pulse rate)	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: beats/min				
arithmetic mean (standard deviation)				
Pulse Rate - Screening - Day -15/-1	71.5 (± 7.4)	76.1 (± 11)		
Pulse Rate - Visit 2 - Day 1 - Pre-dose	75.3 (± 11)	74.5 (± 10.4)		
Pulse Rate - Visit 2 - Day 1 - Post-dose	66.7 (± 7.7)	66.6 (± 9.5)		
Pulse Rate - Visit 3 - Day 8±1 - Pre-dose	77.9 (± 10.7)	76.1 (± 10.4)		
Pulse Rate - Visit 3 - Day 8±1 - Post-dose	68.5 (± 8.6)	65.4 (± 9)		
Pulse Rate - Visit 6 - Day 29±1	73.3 (± 10.4)	70.7 (± 12.2)		
Pulse Rate - Final Visit - Day 56±4/ETV	75 (± 8.6)	3.6 (± 11.8)		

Attachments (see zip file)	End Point/Vital signs_Pulse Rate.pdf

Statistical analyses

Statistical analysis title	Vital signs (pulse rate)
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	75
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	53
upper limit	88
Variability estimate	Standard deviation
Dispersion value	8.6

Secondary: Vital signs (Body weight)	
End point title	Vital signs (Body weight)
End point description:	
End point type	Secondary
End point timeframe:	
Vital signs (Body weight)	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: kg				
arithmetic mean (standard deviation)				
Body Weight - Screening - Day -15/-1	70.72 (± 8.71)	73.23 (± 18.34)		
Body Weight - Final Visit - Day 56±4/ETV	70.21 (± 8.88)	73.78 (± 18.13)		

Attachments (see zip file)	End Point/Vital signs_Body Weight.pdf

Statistical analyses

Statistical analysis title	Vital signs (Body weight)
Comparison groups	Group 1 v Group 2

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	70.21
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	54
upper limit	86
Variability estimate	Standard deviation
Dispersion value	8.88

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Visit 2 (Day 1 pre-dose); At home(Days 1 evening – 7±1 evening); Visit 3 (Day 8±1 pre-dose); At home(Days 8±1 -14±1); Visit 4; At home(Days 15±1-21±1); Visit 5, At home (Days 22±1 - 28±1); Visit 6 and Final Visit.

Adverse event reporting additional description:

AEs assessed at home are monitored through a diary.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Group 1

Reporting group description:

Group 1: rhNGF 20 µg/mL: One drop (35 µL) corresponding to 0.70 µg of rhNGF was instilled into each eye twice a day (b.i.d.) every 12±2 h for a total daily dose of 2.8 µg (both eyes), for 28 consecutive days. Total dose was 78.4 µg/28 days. Batch: f14131; expiry: OCT14.
At the end of the 1st study part (Group 1), the primary efficacy and safety parameters were analysed. Dose escalation proceeded with Group 2 since there were no safety findings that could pose unacceptable risks to patients. In detail, the study continued with the dose of 4 µg/mL since at least 2 out of the 3 primary efficacy parameters improved in Group 1.

Reporting group title	Group 2

Reporting group description:

Group 2: rhNGF 4 µg/mL: One drop (35 µL) corresponding to 0.14 µg of rhNGF was instilled into each eye b.i.d. every 12±2 h for a total daily dose of 0.56 µg, for 28 consecutive days. Total dose was 15.68 µg/28 days.

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Musculoskeletal and connective tissue disorders			
Fall	Additional description: The fall was associated with the concussion and headache: these were reported as 3 distinct TEAEs of moderate intensity, of which only the fall was classified as a SAE. The investigator judged that all 3 TEAEs were unrelated to the IMP.		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	15 / 20 (75.00%)	
Injury, poisoning and procedural complications			
Concussion	Additional description: intensity: moderate		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache	Additional description: intensity: moderate only for 1 patients of group 2		
subjects affected / exposed	0 / 20 (0.00%)	5 / 20 (25.00%)	
occurrences (all)	0	0	
Migraine			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Abnormal sensation in eye	Additional description: The abnormal sensation in eye, was not identified as ocular pain by any of the study subjects.		
subjects affected / exposed	4 / 20 (20.00%)	8 / 20 (40.00%)	
occurrences (all)	0	0	
Eye pain	Additional description: The most frequent related TEAE was eye pain, with an overall frequency of 10%.		
subjects affected / exposed	5 / 20 (25.00%)	6 / 20 (30.00%)	
occurrences (all)	0	0	
Eye irritation	Additional description: An intermittent eye irritation, mild in intensity.		
subjects affected / exposed	3 / 20 (15.00%)	7 / 20 (35.00%)	
occurrences (all)	0	0	
Eye pruritus	Additional description: The patient reported an intermittent eye pruritus of mild intensity.		
subjects affected / exposed	2 / 20 (10.00%)	5 / 20 (25.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	3 / 20 (15.00%)	2 / 20 (10.00%)	
occurrences (all)	0	0	
Foreign body sensation in eyes			

subjects affected / exposed	0 / 20 (0.00%)	4 / 20 (20.00%)	
occurrences (all)	0	0	
Photophobia	Additional description: The patient started to report photophobia of mild intensity which persisted during the study and was still ongoing at the end of the study.		
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	
occurrences (all)	0	0	
Lacrimation increased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	0	
Visual impairment	Additional description: intensity: moderate for patient of group 2 intensityt: mild for patients of group 1		
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Asthenopia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Erythema of eyelid			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Eye discharge			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Eye disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Eyelid pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Eyelid sensory disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Ocular discomfort			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Vitreous detachment			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Infections and infestations			
Conjunctivitis bacterial	Additional description: The patient experienced a bacterial conjunctivitis of mild intensity that was resolved.The bacterial infection was not related to the treatment.This AE led the pt to discontinue the study treatment and he brought back to the clinic the unused IMP.		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	0	
Herpes simplex			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported