Clinical trial results:
DOSE-FINDING STUDY TO ASSESS THE SAFETY AND EFFECT OF SYL1001 IN PATIENTS WITH OCULAR PAIN

Summary

EudraCT number	2014-004857-15
Trial protocol	ES EE
Global end of trial date	10 December 2015

Results information

Result version number	v1 (current)
This version publication date	01 March 2017
First version publication date	01 March 2017

Trial information

Trial identification

Sponsor protocol code	SYL1001_III

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sylentis SAU - Grupo PharmaMar
Sponsor organisation address	Parque Tecnológico de Madrid C/Santiago Grisolía nº 2, Tres Cantos, Madrid, Spain, 28760
Public contact	Head of Regulatory Affairs & QP, Sylentis S.A.U., +34 918047667, info@sylentis.com
Scientific contact	Head of Regulatory Affairs & QP, Sylentis S.A.U., +34 918047667, info@sylentis.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	20 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2015
Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Assessment of the analgesic effect of different doses of SYL1001 ophthalmic solution using the scoring of eye pain on the Visual Analogue Scale (VAS) and the scoring of ocular discomfort in the Ocular Surface Disease Index (OSDI) questionnaire.
- Ocular tolerance at the site of administration (cornea and conjunctiva) after 10 days of treatment.

Protection of trial subjects:

The investigators and their collaborators committed to conduct the study in accordance with the ICH guidelines and guidelines for Good Clinical Practice (GCP), with the Declaration of Helsinki (revised version, Fortaleza, October 2013) and the local laws and guidelines of the countries in which the study is being conducted.

Background therapy: -

Evidence for comparator:

In this trial, the same vehicle used in the formulation of the investigational product (PBS) was used as placebo. The use of a placebo group in this clinical trial was justified due to the following facts:
• Pain was a subjective symptom which was difficult to assess and using a placebo was essential to demonstrate the efficacy of the product.
• There was no product of reference for treating this symptom and neither was there any established reference control.
• All patients were strictly monitored and those patients whose condition deteriorated significantly during the study period could leave the study (voluntarily or according to the judgement of the investigator) and commence a treatment that the investigator considered to be most appropriate in each case (see the section regarding concomitant medication).

Actual start date of recruitment	29 June 2015
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	Spain: 43
Country: Number of subjects enrolled	Estonia: 25
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	59
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

68 patints were included from 29/06/2015 to 19/11/2015.

Pre-assignment

Screening details:

≥ 18 years of age, written consent
Usual mild to moderate dry eye symptoms persistent and daily for more than 3 months (OSDI 13 - 70,VAS 2-7)
Eye tests in both eyes: Oxford scale>0, TBUT<10 sec, Schirmer´s test<10 mm/ 5m

Pre-assignment period milestones

Number of subjects started	68
Number of subjects completed	66

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Concomitant medication with analgesic activity: 1
Reason: Number of subjects	Ocular test out of range: 1

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The sponsor provided the vials with the study medication for each patient. Evaluation of the effect and ocular tolerance was performed in both eyes in a masked fashion meaning neither the patients nor the investigational team knew what medication the patients received.
For each patient the sponsor provided single-dose vials with the study medication. The medication should be stored as specified by the Sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients assigned to placebo group received 40 µL of phosphate buffer saline solution for topical application without active ingredient once daily in each eye over a period of 10 days via the ophthalmic route

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

Dosage and administration details:

Patients assigned to placebo group received 40 µL of phosphate buffer saline solution for topical application without active ingredient once daily in each eye over a period of 10 days via the ophthalmic route
Placebo: Supplied in vials of 0.1 mL with ophthalmic solution: NaCl 140 mM, Sodium phosphate 11 mM, pH 7.2 ± 0.5

Arm title	0.375% SYL1001

Arm description:

Patients assigned to 0.357% SYL1001 arm received 40 µL of 0.375% ophthalmic solution (0.15 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).

Arm type	Experimental
Investigational medicinal product name	SYL1001
Investigational medicinal product code	SYL1001
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Chemically synthesized 19-base small interfering oligonucleotide of RNA (siRNA)
- 0.375% SYL1001: Supplied in vials of 0.1 ml with ophthalmic solution: SYL1001 3.75 mg/mL, pH: 7.2 ± 0.5
The patient went daily to the clinical site for the administration of medication to be administered by staff of the investigational team. The dose was administered with a pipette by placing the volume into the conjunctival sac, then closing the eye for about 10-20 seconds.

Arm title	0.75% SYL1001

Arm description:

Patients assigned to 0.75% SYL1001 arm received 40 µL of 0.75% ophthalmic solution (0.30 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).

Arm type	Experimental
Investigational medicinal product name	SYL1001
Investigational medicinal product code	SYL1001
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Chemically synthesized 19-base small interfering oligonucleotide of RNA (siRNA)
- 0.75% SYL1001: Supplied in vials of 0.1 ml with ophthalmic solution: SYL1001 7.5 mg/mL, pH: 7.2 ± 0.5
The patient went daily to the clinical site for the administration of medication to be administered by staff of the investigational team. The dose was administered with a pipette by placing the volume into the conjunctival sac, then closing the eye for about 10-20 seconds.

Number of subjects in period 1[1]	Placebo	0.375% SYL1001	0.75% SYL1001
Started	24	21	21
Completed	24	21	20
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two patients were not randomized and these patients were excluded from study

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients assigned to placebo group received 40 µL of phosphate buffer saline solution for topical application without active ingredient once daily in each eye over a period of 10 days via the ophthalmic route	
Reporting group title	0.375% SYL1001
Reporting group description:	
Patients assigned to 0.357% SYL1001 arm received 40 µL of 0.375% ophthalmic solution (0.15 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	0.75% SYL1001
Reporting group description:	
Patients assigned to 0.75% SYL1001 arm received 40 µL of 0.75% ophthalmic solution (0.30 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	

Reporting group values	Placebo	0.375% SYL1001	0.75% SYL1001
Number of subjects	24	21	21
Age categorical Units: Subjects			
Adults (18-64 years)	21	18	19
From 65-84 years	3	3	2
Age continuous Units: years			
median	48	47	46
full range (min-max)	26 to 76	19 to 72	38 to 52
Gender categorical Units: Subjects			
Female	22	18	17
Male	2	3	4
Race Units: Subjects			
Caucasian	23	21	20
Hispanic	1	0	1
Relevant medical condition Units: Subjects			
Yes	12	9	13
No	12	12	8
Relevant ocular procedure Units: Subjects			
Yes	2	2	0
No	22	19	21
Relevant systemic procedure Units: Subjects			
Yes	7	4	7
No	17	17	14
Urine analysis Units: Subjects			
Positive	9	7	11

Negative	15	14	10
Hyperemia - Rigth eye Units: Subjects			
Normal	16	8	10
Abnormal	8	13	11
Hyperemia - Left eye Units: Subjects			
Normal	16	9	10
Abnormal	8	12	11
Corneal fluorescein staining - Right eye			
Oxford scale			
Units: Subjects			
Oxford I	17	15	16
Oxford II	6	5	5
Oxford III	1	1	0
Corneal fluorescein staining - Left eye			
Oxford scale			
Units: Subjects			
Oxford I	16	14	16
Oxford II	6	5	5
Oxford III	2	2	0
Blepharitis - Right eye Units: Subjects			
Present	14	8	10
Absent	10	13	11
Blepharitis - Left eye Units: Subjects			
Present	14	8	10
Absent	10	13	11
Altered eyelashes - Right eye Units: Subjects			
Present	1	4	0
Absent	23	17	21
Altered eyelashes - Left eye Units: Subjects			
Present	2	4	0
Absent	22	17	21
Correct blinking and eyelid closure - Right eye Units: Subjects			
Correct	22	21	21
Incorrect	2	0	0
Correct blinking and eyelid closure - left eye Units: Subjects			
Correct	22	21	21
Incorrect	2	0	0
Tear meniscus - Right eye Units: Subjects			
Normal	8	6	10
Thin	16	15	11
Tear meniscus - Left eye			

Units: Subjects			
Normal	8	7	6
Thin	16	14	15
Weight			
Units: Kg			
median	64.4	67	60.5
full range (min-max)	42.5 to 108	48 to 90.9	45 to 95
Height			
Units: meters			
median	1.62	1.63	1.67
full range (min-max)	1.48 to 1.82	1.56 to 1.87	1.45 to 1.85
BMI			
Body mass index			
Units: Kg/m2			
median	24.6	23.6	22.4
full range (min-max)	19.1 to 38.9	19.5 to 34.2	19 to 30.1
SBP			
sistolic blood pressure			
Units: mmHg			
median	120.5	120	120
full range (min-max)	80 to 150	100 to 158	90 to 130
DBP			
Diastolic blood pressure			
Units: mmHg			
median	74	75	73
full range (min-max)	60 to 90	60 to 109	60 to 89
HR			
Heart rate			
Units: ppm			
median	70.5	66	68
full range (min-max)	61 to 94	60 to 99	60 to 92
Temperature			
Units: Centigrades			
median	36.5	36.5	36.5
full range (min-max)	35.5 to 36.8	36 to 36.9	35.5 to 36.8
Leucocytes			
Units: 10^3/µL			
median	5.84	6.2	6
full range (min-max)	4 to 10.7	4.6 to 9.5	2.8 to 8.8
Neutrophils			
Units: 10^3/µL			
median	3.25	3.3	3.18
full range (min-max)	1.62 to 6.38	2.19 to 5	1.6 to 4.53
Neutrophils			
Units: Percentage			
median	53.95	52.9	52.2
full range (min-max)	35.4 to 67.1	33.3 to 63.4	33.4 to 62.1
Lymphocytes			
Units: 10^3/µL			
median	2.21	2.09	2.06
full range (min-max)	1.3 to 3.3	1.3 to 3.97	0.8 to 3.19

Lymphocytes			
Units: Percentage			
median	36	34.1	33.7
full range (min-max)	22 to 54.8	22.3 to 47.1	21 to 50
Monocytes			
Units: 10^3/µL			
median	0.46	0.52	0.5
full range (min-max)	0.2 to 0.86	0.37 to 0.8	0.28 to 0.91
Monocytes			
Units: Percentages			
median	7.95	8.6	8.4
full range (min-max)	3.9 to 11.1	6.07 to 12.7	5.3 to 12.1
Eosinophils			
Units: 10^3/µL			
median	0.14	0.2	0.2
full range (min-max)	0.08 to 0.53	0 to 0.43	0 to 0.63
Eosinophils			
Units: Percentages			
median	2.55	2.9	3.1
full range (min-max)	1.14 to 6.1	0.7 to 6.5	0.6 to 9.9
Basophils			
Units: 10^3/µL			
median	0.04	0.04	0.04
full range (min-max)	0 to 0.1	0 to 0.1	0 to 0.1
Basophils			
Units: Percentages			
median	0.7	0.6	0.7
full range (min-max)	0.2 to 1.3	0.2 to 1.2	0.3 to 1.7
RBC			
Red blood cells			
Units: 10^6/µL			
median	4.58	4.74	4.63
full range (min-max)	4.1 to 5.48	4.15 to 5.44	4.04 to 5.96
Haemoglobin			
Units: g/dl			
median	13.6	14.2	13.6
full range (min-max)	12.4 to 16.6	13.1 to 15.5	11.7 to 15.3
Haematocrite			
Units: percent			
median	41.45	42.3	41.3
full range (min-max)	36.4 to 47.2	38.5 to 46.1	37.8 to 45.5
Platelets			
Units: 10^3/µL			
median	253.5	240	251
full range (min-max)	166 to 405	169 to 371	152 to 333
MCV			
Units: fL			
median	90.35	89.6	89.2
full range (min-max)	83.4 to 98.5	83.3 to 99.5	74.5 to 94.7
MCH			
Units: pg			
median	30.05	29.6	29.4

full range (min-max)	26.5 to 32.9	27.3 to 32.6	23.2 to 31.7
MCHC			
Units: g/dl			
median	32.9	33	32.9
full range (min-max)	31.8 to 35.2	23.2 to 34.9	30.5 to 34.4
Creatinine			
Units: mg/dl			
median	0.7	0.72	0.84
full range (min-max)	0.5 to 0.91	0.59 to 1.02	0.5 to 1.19
Glucose			
Units: mg/dl			
median	90	91	86
full range (min-max)	63.33 to 110	68.33 to 106	75 to 98
GOT			
Units: U/l			
median	17	21	17
full range (min-max)	10 to 41	11 to 33	13 to 23
GPT			
Units: U/l			
median	14	17	15
full range (min-max)	7 to 59	7 to 37	9 to 28
GGT			
Units: U/l			
median	14.5	15	18
full range (min-max)	8 to 53	11 to 80	7 to 47
Alkaline phosphatase			
Units: U/l			
median	58.5	53	46
full range (min-max)	34 to 114	34 to 144	31 to 105
Serum bilirubin			
Units: mg/dl			
median	0.51	0.64	0.47
full range (min-max)	0.2 to 1.05	0.35 to 1.23	0.13 to 1.35
OSDI Score			
Ocular Surface Disease Index			
Units: points			
median	46.75	43.8	41.7
full range (min-max)	14.6 to 68.8	14.6 to 68.8	16.7 to 68.8
Ocular vision-related subscore			
Units: points			
median	33.33	25	29.17
full range (min-max)	8.33 to 66.67	4.17 to 75	16.67 to 70.83
Ocular discomfort-related subscore			
Units: points			
median	56.25	54.17	54.17
full range (min-max)	20.83 to 91.67	16.67 to 87.5	16.67 to 87.5
VAS scale - Right eye			
Visual Analogue Scale day 1 Right eye			
Units: points			
median	4.95	5	2
full range (min-max)	1.5 to 7	2 to 7	2 to 7
VAS scale - Left eye			

Visual Analogue Scale day 1 Left eye			
Units: points			
median	4.95	5	5
full range (min-max)	1.1 to 7	2.1 to 7	2 to 7
TBUT - Right eye			
Tear break-up time			
Units: second			
median	6	5	4
full range (min-max)	2 to 8	3 to 8	1 to 8
TBUT - Left eye			
Tear break-up time			
Units: second			
median	5	5	5
full range (min-max)	2 to 9	2 to 8	1 to 8
Schirmer’s test - Right eye			
Units: mm			
median	4	6	8
full range (min-max)	1 to 9	1 to 9	1 to 9
Schirmer’s test - Left eye			
Units: mm			
median	6	7	6
full range (min-max)	0 to 9	2 to 9	1 to 9
IOP - Right eye			
Intraocular pressure			
Units: mmHg			
median	15	15	14
full range (min-max)	10 to 20	10 to 22	10 to 19
IOP - Left eye			
Intraocular pressure			
Units: mmHg			
median	15	15	15
full range (min-max)	10 to 20	10 to 20	10 to 20
Visual acuity - Right eye			
Units: points			
median	1	1	1
full range (min-max)	0.7 to 1	1 to 1	0.8 to 1
Visual acuity - Left eye			
Units: points			
median	1	1	1
full range (min-max)	0.3 to 1	0.9 to 1	0.8 to 1

Reporting group values	Total		
Number of subjects	66		
Age categorical			
Units: Subjects			
Adults (18-64 years)	58		
From 65-84 years	8		
Age continuous			
Units: years			
median			
full range (min-max)	-		

Gender categorical Units: Subjects			
Female	57		
Male	9		
Race Units: Subjects			
Caucasian	64		
Hispanic	2		
Relevant medical condition Units: Subjects			
Yes	34		
No	32		
Relevant ocular procedure Units: Subjects			
Yes	4		
No	62		
Relevant systemic procedure Units: Subjects			
Yes	18		
No	48		
Urine analysis Units: Subjects			
Positive	27		
Negative	39		
Hyperemia - Rigth eye Units: Subjects			
Normal	34		
Abnormal	32		
Hyperemia - Left eye Units: Subjects			
Normal	35		
Abnormal	31		
Corneal fluorescein staining - Right eye			
Oxford scale			
Units: Subjects			
Oxford I	48		
Oxford II	16		
Oxford III	2		
Corneal fluorescein staining - Left eye			
Oxford scale			
Units: Subjects			
Oxford I	46		
Oxford II	16		
Oxford III	4		
Blepharitis - Right eye Units: Subjects			
Present	32		
Absent	34		
Blepharitis - Left eye Units: Subjects			
Present	32		

Absent	34		
Altered eyelashes - Right eye Units: Subjects			
Present	5		
Absent	61		
Altered eyelashes - Left eye Units: Subjects			
Present	6		
Absent	60		
Correct blinking and eyelid closure - Right eye Units: Subjects			
Correct	64		
Incorrect	2		
Correct blinking and eyelid closure - left eye Units: Subjects			
Correct	64		
Incorrect	2		
Tear meniscus - Right eye Units: Subjects			
Normal	24		
Thin	42		
Tear meniscus - Left eye Units: Subjects			
Normal	21		
Thin	45		
Weight Units: Kg median full range (min-max)	- -		
Height Units: meters median full range (min-max)	- -		
BMI			
Body mass index			
Units: Kg/m2 median full range (min-max)	- -		
SBP			
sistolic blood pressure			
Units: mmHg median full range (min-max)	- -		
DBP			
Diastolic blood pressure			
Units: mmHg median full range (min-max)	- -		
HR			
Heart rate			

Units: ppm median full range (min-max)	-		
Temperature Units: Centigrades median full range (min-max)	-		
Leucocytes Units: 10^3/µL median full range (min-max)	-		
Neutrophils Units: 10^3/µL median full range (min-max)	-		
Neutrophils Units: Percentage median full range (min-max)	-		
Lymphocytes Units: 10^3/µL median full range (min-max)	-		
Lymphocytes Units: Percentage median full range (min-max)	-		
Monocytes Units: 10^3/µL median full range (min-max)	-		
Monocytes Units: Percentages median full range (min-max)	-		
Eosinophils Units: 10^3/µL median full range (min-max)	-		
Eosinophils Units: Percentages median full range (min-max)	-		
Basophils Units: 10^3/µL median full range (min-max)	-		
Basophils Units: Percentages median full range (min-max)	-		
RBC			

Red blood cells			
Units: 10^6/µL median full range (min-max)	-		
Haemoglobin Units: g/dl median full range (min-max)	-		
Haematocrite Units: percent median full range (min-max)	-		
Platelets Units: 10^3/µL median full range (min-max)	-		
MCV Units: fL median full range (min-max)	-		
MCH Units: pg median full range (min-max)	-		
MCHC Units: g/dl median full range (min-max)	-		
Creatinine Units: mg/dl median full range (min-max)	-		
Glucose Units: mg/dl median full range (min-max)	-		
GOT Units: U/l median full range (min-max)	-		
GPT Units: U/l median full range (min-max)	-		
GGT Units: U/l median full range (min-max)	-		
Alkaline phosphatase Units: U/l median full range (min-max)	-		

Serum bilirubin Units: mg/dl median full range (min-max)	-		
OSDI Score			
Ocular Surface Disease Index			
Units: points median full range (min-max)	-		
Ocular vision-related subscore Units: points median full range (min-max)	-		
Ocular discomfort-related subscore Units: points median full range (min-max)	-		
VAS scale - Right eye			
Visual Analogue Scale day 1 Right eye			
Units: points median full range (min-max)	-		
VAS scale - Left eye			
Visual Analogue Scale day 1 Left eye			
Units: points median full range (min-max)	-		
TBUT - Right eye			
Tear break-up time			
Units: second median full range (min-max)	-		
TBUT - Left eye			
Tear break-up time			
Units: second median full range (min-max)	-		
Schirmer’s test - Right eye Units: mm median full range (min-max)	-		
Schirmer’s test - Left eye Units: mm median full range (min-max)	-		
IOP - Right eye			
Intraocular pressure			
Units: mmHg median full range (min-max)	-		
IOP - Left eye			
Intraocular pressure			

Units: mmHg median full range (min-max)	-		
Visual acuity - Right eye Units: points median full range (min-max)	-		
Visual acuity - Left eye Units: points median full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients assigned to placebo group received 40 µL of phosphate buffer saline solution for topical application without active ingredient once daily in each eye over a period of 10 days via the ophthalmic route	
Reporting group title	0.375% SYL1001
Reporting group description:	
Patients assigned to 0.357% SYL1001 arm received 40 µL of 0.375% ophthalmic solution (0.15 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	0.75% SYL1001
Reporting group description:	
Patients assigned to 0.75% SYL1001 arm received 40 µL of 0.75% ophthalmic solution (0.30 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who received any study drug (placebo included) and who participated in at least one post-day 0 assessment. This population coincided with the safety population and full analyses set (FAS).	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who adhered to the major criteria in the protocol, all subjects who completed at least one post-day 0 assessment of the primary endpoint, whose study drug administrations' were greater than 75% (8 over 10) and who did not take any analgesic concomitant medication. Additionally patients with findings detected were excluded from PP.	

Primary: Absolute change of OSDI score

End point title	Absolute change of OSDI score
End point description:	
End point type	Primary
End point timeframe:	
Change from day 0 to day 10 post-administration	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: points				
arithmetic mean (confidence interval 95%)	-17.59 (-24 to -11.2)	-16.19 (-24 to -8.4)	-16.45 (-23.8 to -9.1)	

Attachments (see zip file)	OSDI score/OSDI score.bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9839
Method	ANCOVA

Primary: Absolute change of OSDI score (PP)

End point title	Absolute change of OSDI score (PP)

End point description:

End point type	Primary

End point timeframe:

at day 10 post-administration from day 0

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[1]	21	19[2]	
Units: points				
arithmetic mean (confidence interval 95%)	-17.47 (-24.1 to -10.8)	-16.19 (-24 to -8.4)	-17.95 (-25.8 to -10.1)	

Notes:

[1] - PP population

[2] - PP population

Attachments (see zip file)	OSDI score/OSDI score PP.bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.989
Method	ANCOVA

Primary: Absolute changes of VAS score at day 10 pre-administration

End point title	Absolute changes of VAS score at day 10 pre-administration

End point description:

End point type	Primary

End point timeframe:

at day 10 pre-administration (24h after the 9th administration) from day 1

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: points				
arithmetic mean (confidence interval 95%)	-1.65 (-2.09 to -1.22)	-1.58 (-2.04 to -1.12)	-1.55 (-2.01 to -1.09)	

Attachments (see zip file)	VAS score/VAS score.bmp

Statistical analyses

Statistical analysis title	Difference between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9401
Method	ANCOVA

Primary: Absolute change of VAS score at day 10 post-administration

End point title	Absolute change of VAS score at day 10 post-administration

End point description:

End point type	Primary

End point timeframe:

at day 10 post-administration (1h after the 10th administration) from day 1

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: points				
arithmetic mean (confidence interval 95%)	-1.88 (-2.37 to -1.39)	-2.12 (-2.64 to -1.6)	-1.87 (-2.39 to -1.35)	

Attachments (see zip file)	VAS/VAS score.bmp

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7468
Method	ANCOVA

Primary: Absolute changes of VAS score at day 10 pre-administration (PP)

End point title	Absolute changes of VAS score at day 10 pre-administration (PP)

End point description:

End point type	Primary

End point timeframe:

at day 10 pre-administration (24h after the 9th administration) from day 1

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: points				
arithmetic mean (confidence interval 95%)	-1.74 (-2.18 to -1.3)	-1.61 (-2.07 to -1.15)	-1.6 (-2.09 to -1.12)	

Attachments (see zip file)	VAS score/VAS score PP.bmp

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8947
Method	ANCOVA

Primary: Absolute change of VAS score at day 10 post-administration (PP)

End point title	Absolute change of VAS score at day 10 post-administration (PP)

End point description:

End point type	Primary

End point timeframe:

at day 10 post-administration (1h after the 10th administration) from day 1

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: points				
arithmetic mean (confidence interval 95%)	-2.02 (-2.51 to -1.53)	-2.15 (-2.67 to -1.64)	-2.06 (-2.6 to -1.52)	

Attachments (see zip file)	VAS score/VAS score PP.bmp

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	0.375% SYL1001 v 0.75% SYL1001 v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9288
Method	ANCOVA

Primary: Absolute change of VAS score at each day from day 1

End point title	Absolute change of VAS score at each day from day 1

End point description:

End point type	Primary

End point timeframe:

at each day from day 1

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: points				
arithmetic mean (confidence interval 95%)				
Day 2	-0.3 (-0.55 to -0.04)	-0.13 (-0.4 to 0.14)	-0.33 (-0.6 to -0.06)	
Day 3	-0.66 (-1.01 to -0.31)	-0.42 (-0.79 to -0.05)	-0.01 (-0.38 to 0.36)	
Day 4	-0.6 (-0.94 to -0.25)	-0.49 (-0.85 to -0.12)	-0.75 (-1.12 to -0.38)	
Day 5	-0.99 (-1.3 to -0.68)	-0.76 (-1.09 to -0.43)	-0.85 (-1.18 to -0.52)	
Day 6	-1.22 (-1.61 to -0.84)	-0.86 (-1.27 to -0.45)	-1 (-1.41 to -0.59)	
Day 7	-1.46 (-1.83 to -1.09)	-1.24 (-1.63 to -0.84)	-1.23 (-1.63 to -0.84)	
Day 8	-1.65 (-2.05 to -1.25)	-1.25 (-1.68 to -0.82)	-1.26 (-1.69 to -0.84)	
Day 9	-1.6 (-2.03 to -1.17)	-1.45 (-1.91 to -0.99)	-1.6 (-2.06 to -1.14)	
Day 10	-1.65 (-2.09 to -1.22)	-1.58 (-2.04 to -1.12)	-1.55 (-2.01 to -1.09)	
Day 10 post	-1.88 (-2.37 to -1.39)	-2.12 (-2.64 to -1.6)	-1.87 (-2.39 to -1.35)	

Attachments (see zip file)	VAS score/VAS score.bmp

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5441 [3]
Method	ANCOVA

Notes:

[3] - Day 2: 0.5441; Day 3: 0.0419 (Placebo-0.75% SYL1001: dif=-0.65 p=0.0124); Day 4: 0.5980; Day 5: 0.5932; Day 6: 0.4378; Day 7: 0.6284; Day 8: 0.2953; Day 9: 0.8643

Primary: Change of hyperemia

End point title	Change of hyperemia

End point description:

Improvement: patients with abnormal hyperemia at day 0 and normal hyperemia at day 10
Maintenance: patients with: Abnormal Hyperemia at day 0 and Abnormal Hyperemia at Day 10 or Normal Hyperemia at day 0 and Normal Hyperemia at Day 10
Worsening: patients with Normal Hyperemia at day 0 and Abnormal Hyperemia at Day 10
Two measurements (one for each eye) by patient

End point type	Primary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: percent of subjects				
Improvement	2	3	9	
Maintenance	44	37	28	
Worsening	2	2	5	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0294 [4]
Method	Fisher exact

Notes:

[4] - Pairwise comparisons (Bonferroni): 1vs2: 1.0000; 1vs3: 0.0344; 2vs3: 0.1888;

Primary: Change of hyperemia (PP)

End point title	Change of hyperemia (PP)
End point description: Improvement: patients with abnormal hyperemia at day 0 and normal hyperemia at day 10 Maintenance: patients with: Abnormal Hyperemia at day 0 and Abnormal Hyperemia at Day 10 or Normal Hyperemia at day 0 and Normal Hyperemia at Day 10 Worsening: patients with Normal Hyperemia at day 0 and Abnormal Hyperemia at Day 10 Two measurements (one for each eye) by patient	
End point type	Primary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[5]	21[6]	19[7]	
Units: percent of subjects				
Improvement	2	3	9	
Maintenance	42	37	24	
Worsening	2	2	5	

Notes:
[5] - Two measurements (one for each eye) by patient
[6] - Two measurements (one for each eye) by patient
[7] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 [8]
Method	Fisher exact

Notes:
[8] - Pairwise comparisons (Bonferroni): 1vs2: 1.0000; 1vs3: 0.0204; 2vs3: 0.0965;

Primary: Change of corneal staining

End point title	Change of corneal staining

End point description:

Two measurements (one for each eye) by patient
Improvement of Corneal fluorescein staining: improve at least one degree the Oxford scale

End point type	Primary

End point timeframe:

at day 10 from day 0

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[9]	21[10]	21[11]	
Units: number of subjects				
Improvement	25	19	19	
Maintenance	23	20	23	
Worsening	0	3	0	

Notes:
[9] - Two measurements (one for each eye) by patient
[10] - Two measurements (one for each eye) by patient
[11] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1355
Method	Chi-squared

Primary: Change of corneal staining (PP)

End point title	Change of corneal staining (PP)

End point description:

Improvement of Corneal fluorescein staining: improve at least one degree the Oxford scale

End point type	Primary

End point timeframe:

at day 10 from day 0

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[12]	21[13]	19[14]	
Units: number of subjects				
Improvement	23	19	17	
Maintenance	23	20	21	
Worsening	0	3	0	

Notes:

[12] - Two measurements (one for each eye) by patient

[13] - Two measurements (one for each eye) by patient

[14] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1715
Method	Chi-squared

Secondary: Change of Blepharitis

End point title	Change of Blepharitis

End point description:

Improvement: patient with present at day 0 and absent at day 10

End point type	Secondary

End point timeframe:

at day 10 from day 0

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[15]	21[16]	21[17]	
Units: number of subjects				
Improvement	8	6	8	
Maintenance	36	34	32	
Worsening	4	2	2	

Notes:

[15] - Two measurements (one for each eye) by patient

[16] - Two measurements (one for each eye) by patient

[17] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Secondary: Change of Blepharitis (PP)

End point title	Change of Blepharitis (PP)
End point description:	
Improvement: patient with present at day 0 and absent at day 10	
End point type	Secondary
End point timeframe:	
at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[18]	21[19]	19[20]	
Units: number of subjects				
Improvement	8	6	8	
Maintenance	34	34	28	
Worsening	4	2	2	

Notes:

[18] - Two measurements (one for each eye) by patient

[19] - Two measurements (one for each eye) by patient

[20] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9729
Method	Chi-squared

Secondary: Altered eyelashes

End point title	Altered eyelashes
End point description: Improvement: patient with present at day 0 and absent at day 10	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[21]	21[22]	21[23]	
Units: number of subjects				
Improvement	3	6	0	
Maintenance	45	34	40	
Worsening	0	2	2	

Notes:

[21] - Two measurements (one for each eye) by patient

[22] - Two measurements (one for each eye) by patient

[23] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2845
Method	Chi-squared

Secondary: Altered eyelashes (PP)

End point title	Altered eyelashes (PP)
End point description: Improvement: patient with present at day 0 and absent at day 10	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[24]	21[25]	19[26]	
Units: number of subjects				
Improvement	3	6	0	
Maintenance	43	34	36	
Worsening	0	2	2	

Notes:
[24] - Two measurements (one for each eye) by patient
[25] - Two measurements (one for each eye) by patient
[26] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3466
Method	Chi-squared

Secondary: Tear meniscus

End point title	Tear meniscus
End point description: Improvement: patient with thin at day 0 and normal at day 10	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[27]	21[28]	21[29]	
Units: number of subjects				
Improvement	8	9	7	
Maintenance	38	31	29	
Worsening	2	2	6	

Notes:

[27] - Two measurements (one for each eye) by patient

[28] - Two measurements (one for each eye) by patient

[29] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7023
Method	Chi-squared

Secondary: Tear meniscus (PP)

End point title	Tear meniscus (PP)

End point description:

End point type	Secondary

End point timeframe:

at day 10 from day 0

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[30]	21[31]	19[32]	
Units: number of subjects				
Improvement	6	9	7	
Maintenance	38	31	27	
Worsening	2	2	4	

Notes:

[30] - Two measurements (one for each eye) by patient

[31] - Two measurements (one for each eye) by patient

[32] - Two measurements (one for each eye) by patient

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	0.375% SYL1001 v Placebo v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7182
Method	Chi-squared

Secondary: Change of IOP

End point title	Change of IOP
End point description: Intraocular pressure	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: mmHg				
arithmetic mean (confidence interval 95%)	-1.03 (-1.55 to -0.5)	-0.41 (-0.96 to 0.15)	-0.52 (-1.07 to 0.04)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	ANCOVA

Secondary: Change of IOP (PP)	
End point title	Change of IOP (PP)
End point description: Intraocular pressure	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: mmHg				
arithmetic mean (confidence interval 95%)	-1.08 (-1.63 to -0.54)	-0.41 (-0.96 to 0.15)	-0.53 (-1.12 to 0.06)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1979
Method	ANCOVA

Secondary: Change of BCVA	
End point title	Change of BCVA
End point description: Visual acuity	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: points				
arithmetic mean (confidence interval 95%)	-0.02 (-0.04 to -0.01)	-0.01 (-0.03 to 0.01)	0 (-0.02 to 0.01)	

Statistical analyses

Statistical analysis title	Change of BCVA
Comparison groups	0.375% SYL1001 v 0.75% SYL1001 v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3075
Method	Chi-squared

Secondary: Change of BCVA (PP)	
End point title	Change of BCVA (PP)
End point description: Visual acuity	
End point type	Secondary
End point timeframe: at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: points				
arithmetic mean (confidence interval 95%)	-0.02 (-0.04 to -0.01)	-0.01 (-0.03 to 0.01)	-0.01 (-0.03 to 0.02)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3103
Method	ANCOVA

Secondary: Change of TBUT	
End point title	Change of TBUT
End point description:	
End point type	Secondary
End point timeframe:	
at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: second				
arithmetic mean (confidence interval 95%)	0.13 (-0.63 to 0.88)	0.14 (-0.67 to 0.95)	1.31 (0.5 to 2.12)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 [33]
Method	ANCOVA

Notes:

[33] - Placebo vs 0.75% SYL1001 dif: -1.18 CI95% (-2.29, -0.07) p=0.0367
0.375% SYL1001 vs 0.75% SYL1001 dif: -1.17 CI95% (-2.31, -0.03) p=0.0449

Secondary: Change of TBUT (PP)	
End point title	Change of TBUT (PP)
End point description:	
Tear break-up time	
End point type	Secondary
End point timeframe:	
at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: second				
arithmetic mean (confidence interval 95%)	0.27 (-0.5 to 1.05)	0.14 (-0.67 to 0.95)	1.4 (0.55 to 2.26)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 [34]
Method	ANCOVA

Notes:

[34] - Placebo vs 0.75% SYL1001 dif: -1.13 CI95%(-2.28, 0.02) p=0.0548
0.375% SYL1001 vs 0.75% SYL1001 dif: -1.26 CI95% (-2.44, -0.09) p=0.0357

Secondary: Change of Schirmer´s test

End point title	Change of Schirmer´s test
End point description:	
End point type	Secondary
End point timeframe:	
at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: mm				
arithmetic mean (confidence interval 95%)	0.36 (-0.58 to 1.31)	0.74 (-0.27 to 1.75)	0.82 (-0.19 to 1.83)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7831
Method	ANCOVA

Secondary: Change of Schirmer´s test (PP)	
End point title	Change of Schirmer´s test (PP)
End point description:	
End point type	Secondary
End point timeframe:	
at day 10 from day 0	

End point values	Placebo	0.375% SYL1001	0.75% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	19	
Units: mm				
arithmetic mean (confidence interval 95%)	-0.06 (-0.97 to 0.86)	0.75 (-0.2 to 1.69)	1.16 (0.16 to 2.16)	

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Placebo v 0.375% SYL1001 v 0.75% SYL1001
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1987
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients assigned to placebo group received 40 µL of phosphate buffer saline solution for topical application without active ingredient once daily in each eye over a period of 10 days via the ophthalmic route	
Reporting group title	0.375% SYL1001
Reporting group description:	
Patients assigned to 0.357% SYL1001 arm received 40 µL of 0.375% ophthalmic solution (0.15 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	0.75% SYL1001
Reporting group description:	
Patients assigned to 0.75% SYL1001 arm received 40 µL of 0.75% ophthalmic solution (0.30 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	

Serious adverse events	Placebo	0.375% SYL1001	0.75% SYL1001
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo	0.375% SYL1001	0.75% SYL1001
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 24 (12.50%)	0 / 21 (0.00%)	2 / 21 (9.52%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Eye disorders			

Eye pain subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	0 / 21 (0.00%) 0	0 / 21 (0.00%) 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