Clinical trial results:
Pilot study to assess the safety and effect of SYL1001 in patients with ocular pain

Summary

EudraCT number	2012-001177-93
Trial protocol	ES
Global end of trial date	30 April 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_II

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	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Compare the analgesic effect of SYL1001 versus placebo
- Compare the tolerability on the ocular surface (cornea and conjunctiva) in the treatment of ocular pain associated with dry eye syndrome.

Protection of trial subjects:

The investigators and their collaborators undertook to accurately comply with the instructions of the Spanish Medical Deontological Code, the Declaration of Helsinki and the National Guidelines regarding clinical trials in humans (Royal Decree 223/2004, of 6 February). Furthermore, the study was conducted in accordance with the European Good Clinical Practice (CGP) guidelines.

Background therapy: -

Evidence for comparator:

Evidence for comparator:
In this trial, the same vehicle was used in the formulation of the investigational product (PBS) 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 currently 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 considers to be most appropriate in each case (see the section regarding concomitant medication).

Actual start date of recruitment	01 October 2012
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: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	45
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

61 patients were included from 18/02/2013 to 08/04/2015

Pre-assignment

Screening details:

≥ 18 years; IC sign;mild to moderate dry eye symptoms (OSDI 13-70 and VAS2-7);Eye tests in both eyes (Oxford>0,TBUT<10 sec, Schirmer´s test<10 mm/ 5m)

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	Investigator, Monitor, Subject

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	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

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	1.125% SYL1001

Arm description:

Patients assigned to 1.125% SYL1001 arm received 40 µL of 1.125% ophthalmic solution (0.45 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:

This group received 40 µL of SYL1001 ophthalmic solution in both eyes. SYL1001 is a chemically synthesized 19-base small interfering oligonucleotide of RNA (siRNA) targeted to human Transient Receptor Potential Vanilloid 1 (TRPV1)

Arm title	2.25% SYL1001

Arm description:

Patients assigned to any of the two SYL1001 arms received 40 µL of 2.25% ophthalmic solution (0.90 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:

This group received 40 µL of SYL1001 ophthalmic solution in both eyes. SYL1001 is a chemically synthesized 19-base small interfering oligonucleotide of RNA (siRNA) targeted to human Transient Receptor Potential Vanilloid 1 (TRPV1)

Number of subjects in period 1[1]	Placebo	1.125% SYL1001	2.25% SYL1001
Started	20	20	20
Completed	20	20	19
Not completed	0	0	1
Consent withdrawn by subject	-	-	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: One patient was excluded because this patient was not treated

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	1.125% SYL1001
Reporting group description:	
Patients assigned to 1.125% SYL1001 arm received 40 µL of 1.125% ophthalmic solution (0.45 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	2.25% SYL1001
Reporting group description:	
Patients assigned to any of the two SYL1001 arms received 40 µL of 2.25% ophthalmic solution (0.90 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	

Reporting group values	Placebo	1.125% SYL1001	2.25% SYL1001
Number of subjects	20	20	20
Age categorical Units: Subjects			
Adults (18-64 years)	17	15	13
From 65-84 years	3	5	7
Age continuous Units: years			
median	40.39	45.83	60.67
full range (min-max)	23.56 to 75.38	27.36 to 76.35	27.89 to 78.23
Gender categorical Units: Subjects			
Female	15	17	18
Male	5	3	2
Hyperemia - Right eye Units: Subjects			
Normal	11	7	15
Abnormal	9	13	5
Hyperemia - Left eye Units: Subjects			
Normal	12	8	15
Abnormal	8	12	5
Corneal fluorescein staining - Right eye Units: Subjects			
Oxford I	14	12	13
Oxford II	5	7	6
Oxford III	1	1	1
Corneal fluorescein staining - Left eye Units: Subjects			
Oxford I	13	11	13
Oxford II	6	8	6
Oxford III	1	1	1
Blepharitis - Right eye			

Units: Subjects			
Present	11	11	13
Absent	9	9	7
Blepharitis - Left eye Units: Subjects			
Present	11	11	13
Absent	9	9	7
Correct blinking and eyelid closure - Right eye Units: Subjects			
Correct	20	19	20
Incorrect	0	1	0
Correct blinking and eyelid closure - Left eye Units: Subjects			
Correct	20	19	20
Incorrect	0	1	0
Tear meniscus - Right eye Units: Subjects			
Normal	9	9	5
Thin	11	11	15
Tear meniscus - Left eye Units: Subjects			
Normal	9	9	5
Thin	11	11	15
SBP			
SBP=sistolic blood pressure			
Units: mmHg			
median	111	116.5	112.5
full range (min-max)	90 to 147	90 to 140	82 to 139
DBP			
DBP=Diastolic blood pressure			
Units: mmHg			
median	70	70	71.5
full range (min-max)	50 to 91	60 to 87	57 to 86
Heart rate Units: bpm			
median	74	71	73
full range (min-max)	51 to 96	48 to 82	55 to 89
OSDI score			
OSDI: Ocular surface disease index			
Units: points			
median	37.5	39.12	43.75
full range (min-max)	22.9 to 70	13 to 62.5	20.45 to 63.64
VAS score - Right eye			
VAS: Visual analogue scale			
Units: points			
median	5	5	5
full range (min-max)	2 to 7	2 to 7	2 to 7
VAS score - Left eye			
VAS: Visual analogue scale			
Units: points			

median	5	5.9	5.25
full range (min-max)	2 to 7	2 to 7	2 to 7
TBUT - Right eye			
TBUT = Tear break-up time			
Units: second			
median	5	4	4
full range (min-max)	2 to 9	1 to 9	1 to 8
TBUT - Left eye			
TBUT= Tear break-up time			
Units: second			
median	6	4	4
full range (min-max)	1 to 9	1 to 9	1 to 8
Schirmer’s test - Right eye			
Schirmer’s test with anesthesia			
Units: mm			
median	5	4.5	4
full range (min-max)	0 to 9	1 to 9	1 to 9
Schirmer’s test - Left eye			
Schirmer’s test with anesthesia			
Units: mm			
median	6	5	5.5
full range (min-max)	1 to 9	0 to 9	1 to 9
IOP - Right eye			
IOP= intraocular pressure			
Units: mmHg			
median	14	16	14.5
full range (min-max)	10 to 18	10 to 19	8 to 19
IOP - Left eye			
IOP= intraocular pressure			
Units: mmHg			
median	13	16	15
full range (min-max)	10 to 17	11 to 21	6 to 19
Visual acuity - Right eye			
Units: points			
median	1	1	1
full range (min-max)	0.4 to 1.2	0.5 to 1	0.7 to 1.25
Visual acuity - Left eye			
Units: units			
median	1	1	1
full range (min-max)	0.7 to 1.2	0.5 to 1.2	0.9 to 1.25

Reporting group values	Total		
Number of subjects	60		
Age categorical			
Units: Subjects			
Adults (18-64 years)	45		
From 65-84 years	15		
Age continuous			
Units: years			
median			
full range (min-max)	-		

Gender categorical Units: Subjects			
Female	50		
Male	10		
Hyperemia - Right eye Units: Subjects			
Normal	33		
Abnormal	27		
Hyperemia - Left eye Units: Subjects			
Normal	35		
Abnormal	25		
Corneal fluorescein staining - Right eye Units: Subjects			
Oxford I	39		
Oxford II	18		
Oxford III	3		
Corneal fluorescein staining - Left eye Units: Subjects			
Oxford I	37		
Oxford II	20		
Oxford III	3		
Blepharitis - Right eye Units: Subjects			
Present	35		
Absent	25		
Blepharitis - Left eye Units: Subjects			
Present	35		
Absent	25		
Correct blinking and eyelid closure - Right eye Units: Subjects			
Correct	59		
Incorrect	1		
Correct blinking and eyelid closure - Left eye Units: Subjects			
Correct	59		
Incorrect	1		
Tear meniscus - Right eye Units: Subjects			
Normal	23		
Thin	37		
Tear meniscus - Left eye Units: Subjects			
Normal	23		
Thin	37		
SBP			
SBP=sistolic blood pressure			
Units: mmHg median			

full range (min-max)	-		
DBP			
DBP=Diastolic blood pressure			
Units: mmHg median full range (min-max)	-		
Heart rate Units: bpm median full range (min-max)	-		
OSDI score			
OSDI: Ocular surface disease index			
Units: points median full range (min-max)	-		
VAS score - Right eye			
VAS: Visual analogue scale			
Units: points median full range (min-max)	-		
VAS score - Left eye			
VAS: Visual analogue scale			
Units: points median full range (min-max)	-		
TBUT - Right eye			
TBUT = Tear break-up time			
Units: second median full range (min-max)	-		
TBUT - Left eye			
TBUT= Tear break-up time			
Units: second median full range (min-max)	-		
Schirmer’s test - Right eye			
Schirmer’s test with anesthesia			
Units: mm median full range (min-max)	-		
Schirmer’s test - Left eye			
Schirmer’s test with anesthesia			
Units: mm median full range (min-max)	-		
IOP - Right eye			
IOP= intraocular pressure			
Units: mmHg median full range (min-max)	-		
IOP - Left eye			
IOP= 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: units 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	1.125% SYL1001
Reporting group description:	
Patients assigned to 1.125% SYL1001 arm received 40 µL of 1.125% ophthalmic solution (0.45 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	2.25% SYL1001
Reporting group description:	
Patients assigned to any of the two SYL1001 arms received 40 µL of 2.25% ophthalmic solution (0.90 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:	
OSDI=Ocular surface disease index	
End point type	Primary
End point timeframe:	
Change from day 0 to day 10 post-administration	

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: points				
arithmetic mean (confidence interval 95%)	-12.51 (-19 to -6)	-15.15 (-21.7 to -8.6)	-7.6 (-14.2 to -1)	

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

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2763
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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: points				
arithmetic mean (confidence interval 95%)	-12.37 (-19.2 to -5.5)	-15.2 (-21.8 to -8.6)	-11.38 (-19.3 to -3.5)	

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

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7298
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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: points				
arithmetic mean (confidence interval 95%)	-0.98 (-1.5 to -0.4)	-1.97 (-2.5 to -1.4)	-1.1 (-1.7 to -0.5)	

Attachments (see zip file)	VAS score/VAS score pre-adm.bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0255 [1]
Method	ANCOVA

Notes:

[1] - Placebo vs 1.125% SYL1001: Dif 0.99 95%CI (0.2, 1.8) p=0.0127
Placebo vs 2.25% SYL1001: Dif 0.13 95%CI (-0.7, 0.9) p=0.7457
1.125% SYL1001 vs 2.25% SYL1001: Dif -0.87 95%CI (-1.7, 0.1) p=0.0300

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:

Due to protocol deviations, only 38 out of 60 patients could be included in this analysis. 22 patients did not have the measurement at day 10 post-treatment

End point type	Primary

End point timeframe:

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

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	17	11	
Units: points				
arithmetic mean (confidence interval 95%)	-1.61 (-2.32 to -0.89)	-2.24 (-2.83 to -1.64)	-2.38 (-3.2 to -1.55)	

Attachments (see zip file)	VAS score/VAS score post-adm.bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	ANCOVA

Primary: Absolute change at day 10 post-treatment (imputation)

End point title	Absolute change at day 10 post-treatment (imputation)

End point description:

Due to missing data at day 10 post-treatment, the change of the VAS scored was imputed using a imputation method which if VAS value at day 10 post-treatment was missing, it was set to the global mean VAS value in the corresponding treatment group (for all subjects) during the treatment period.

End point type	Primary

End point timeframe:

at day 10 post-treatment from day 1

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: points				
arithmetic mean (confidence interval 95%)	-1.55 (-2 to -1.1)	-2.35 (-2.8 to -1.9)	-2.65 (-3.1 to -2.2)	

Attachments (see zip file)	VAS score/VAS score post-adm (imp).bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [2]
Method	ANCOVA

Notes:

[2] - Placebo vs 1.125% SYL1001: Dif 0.80 95%CI (0.2, 1.4) p=0.0160
Placebo vs 2.25% SYL1001: Dif 1.01 95%CI (0.5, 1.7) p=0.0010
1.125% SYL1001 vs 2.25% SY1001: Dif 0.30 95%CI (-0.3, 0.9) p=0.3520

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: points				
arithmetic mean (confidence interval 95%)	-1.21 (-1.7 to -0.7)	-1.98 (-2.5 to -1.5)	-1.46 (-2.1 to -0.9)	

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

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	ANCOVA

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

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

End point description:

End point type	Primary

End point timeframe:

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

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	17	8	
Units: points				
arithmetic mean (confidence interval 95%)	-1.44 (-2.2 to -0.7)	-2.27 (-2.9 to -1.7)	-2.51 (-3.4 to -1.6)	

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

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137
Method	ANCOVA

Primary: Absolute change at day 10 post-treatment (imputation) (PP)

End point title	Absolute change at day 10 post-treatment (imputation) (PP)

End point description:

Due to missing data at day 10 post-treatment, the change of the VAS score was imputed using a imputation method which if VAS value at day 10 post-treatment was missing, it was set to the global mean VAS value in the corresponding treatment group (for all subjects) during the treatment period.

End point type	Primary

End point timeframe:

at day 10 post-treatment from day 1 using imputation method

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: points				
arithmetic mean (confidence interval 95%)	-1.42 (-1.9 to -0.9)	-2.4 (-2.9 to -1.9)	-2.79 (-3.3 to -2.2)	

Attachments (see zip file)	VAS score/VAS score post-adm (imp) (PP).bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [3]
Method	ANCOVA

Notes:

[3] - Placebo vs 1.125% SYL1001: Dif 0.97 95%CI (0.3, 1.6) p=0.0060
Placebo vs 2.25% SYL1001: Dif 1.37 95%CI (0.6, 2.1) p=0.0010
1.125% SYL1001vs 2.25% SYL1001: Dif 0.40 95%CI (-0.3, 1.1) p=0.2710

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:

During the first three days of treatment, there were not significant differences between treatments. From day 4 until the end of treatment, the decrease of VAS was significantly higher in 1.125% SYL1001 compared to placebo.

End point type	Primary

End point timeframe:

at each day from day 1

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: points				
arithmetic mean (confidence interval 95%)				
Day 2	-0.58 (-1 to -0.1)	-0.06 (-0.5 to 0.4)	0.27 (-0.2 to 0.7)	
Day 3	-0.31 (-0.8 to 0.2)	-0.47 (-1 to 0.1)	0.08 (-0.5 to 0.6)	
Day 4	-0.61 (-1.1 to 0.1)	-1.27 (-1.8 to 0.8)	-0.04 (-0.5 to 0.5)	
Day 5	-0.7 (-1.2 to -0.2)	-1.46 (-1.9 to -1)	-0.43 (-0.9 to 0)	
Day 6	-0.88 (-1.4 to -0.4)	-1.8 (-2.3 to -1.3)	-0.72 (-1.2 to -0.2)	
Day 7	-0.87 (-1.4 to -0.4)	-2.02 (-2.5 to -1.5)	-1.06 (-1.6 to -0.6)	

Day 8	-0.68 (-1.3 to -0.1)	-1.92 (-2.5 to -1.3)	-0.91 (-1.5 to -0.3)	
Day 9	-0.9 (-1.5 to -0.3)	-1.92 (-2.5 to -1.3)	-1.04 (-1.6 to -0.4)	
Day 10	-0.98 (-1.5 to -0.4)	-1.97 (-2.5 to -1.4)	-1.1 (-1.7 to -0.5)	
Day 10 post	-1.55 (-2 to -1.1)	-2.35 (-2.8 to -1.9)	-2.65 (-3.1 to -2.2)	

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

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	1.125% SYL1001 v Placebo v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4222 [4]
Method	ANCOVA

Notes:

[4] - Pb-1.125% SYL1001: p (Dif CI95%)
Day 2: 0.4222; Day 3: 0.6743; Day 4: 0.0633; Day 5: 0.0253 (0.76 (0.1,1.4)); Day 6: 0.0105 (0.91 (0.2,1.6)); Day 7: 0.0016 (1.15 (0.4,1.9)); Day 8: 0.0029 (1.24 (0.4,2.1)); Day 9: 0.0181 (1.02 (0.2,1.9)

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: Number				
Improvement	7	20	4	
Maintenance	29	15	34	
Worsening	4	5	2	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [5]
Method	Chi-squared

Notes:

[5] - Pairwise comparisons (Bonferroni): 1vs2: 0.0134; 1vs3: 1.0000; 2vs3: 0.0002;

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: Number				
Improvement	5	20	0	
Maintenance	29	15	28	
Worsening	2	5	0	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [6]
Method	Chi-squared

Notes:

[6] - Pairwise comparisons (Bonferroni): 1vs2: 0.0021; 1vs3: 0.1412; 2vs3: 0.0001;

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: Number				
Improvement	18	27	22	
Maintenance	18	12	18	
Worsening	4	1	0	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0743 [7]
Method	Chi-squared

Notes:

[7] - Improvement at least 2 degrees Oxford scale p-value=0.0012 (Pairwise comparisons (Bonferroni): 1vs2: 0.0542; 1vs3: 0.7057; 2vs3: 0.0024)

Primary: Change of corneal staining (PP)

End point title	Change of corneal staining (PP)

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: Number				
Improvement	16	27	14	
Maintenance	16	12	14	
Worsening	4	1	0	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0713 [8]
Method	Chi-squared

Notes:

[8] - Improvement at least 2 degrees Oxford scale p-value=0.0008 (Pairwise comparisons (Bonferroni): 1vs2: 0.0160; 1vs3: 1.0000; 2vs3: 0.0063)

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
Two measurements (one for each eye) by patient

End point type	Secondary

End point timeframe:

at day 10 from day 0

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: Number				
Improvement	6	8	4	
Maintenance	33	26	32	
Worsening	1	6	4	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6755
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
Two measurements (one for each eye) by patient

End point type	Secondary

End point timeframe:

at day 10 from day 0

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: Number				
Improvement	6	8	0	
Maintenance	29	26	26	
Worsening	1	6	2	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1523
Method	Chi-squared

Secondary: Tear meniscus

End point title	Tear meniscus

End point description:

Two measurements (one for each eye) by patient
Improvement: patient with thin at day 0 and normal at day 10

End point type	Secondary

End point timeframe:

at day 10 post-treatment from day 0

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: Number				
Improvement	13	8	9	
Maintenance	24	26	31	
Worsening	3	6	0	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	1.125% SYL1001 v 2.25% SYL1001 v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5506
Method	Chi-squared

Secondary: Tear meniscus (PP)

End point title	Tear meniscus (PP)

End point description:

Two measurements (one for each eye) by patient
Improvement: patient with thin at day 0 and normal at day 10

End point type	Secondary

End point timeframe:

at day 10 post-treatment from day 0

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: Number				
Improvement	11	8	6	
Maintenance	22	26	22	
Worsening	3	6	0	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	1.125% SYL1001 v 2.25% SYL1001 v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5832
Method	Chi-squared

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

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: mmHg				
arithmetic mean (confidence interval 95%)	-0.24 (-0.8 to 0.4)	-0.29 (-0.9 to 0.3)	-0.93 (-1.6 to -0.3)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2573
Method	ANCOVA

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

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: mmHg				
arithmetic mean (confidence interval 95%)	-0.55 (-1.2 to 0.1)	-1.12 (-1.8 to -0.5)	-0.32 (-1.1 to 0.4)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2525
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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: points				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0.02 (0 to 0.021)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.641
Method	ANCOVA

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: points				
arithmetic mean (confidence interval 95%)	-0.01 (-0.011 to 0)	0 (0 to 0)	0.01 (0 to 0.011)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3721
Method	ANCOVA

Secondary: Change of TBUT

End point title	Change of TBUT
End point description: TBUT=tear break-up time	
End point type	Secondary
End point timeframe: at day 10 post-treatment from day 0	

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: seconds				
arithmetic mean (confidence interval 95%)	0.75 (-0.4 to 1.9)	1.85 (0.7 to 3)	0.56 (-0.5 to 1.7)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2192
Method	ANCOVA

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: seconds				
arithmetic mean (confidence interval 95%)	0.49 (-0.7 to 1.7)	1.84 (0.7 to 2.9)	0.47 (-0.8 to 1.8)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1668
Method	ANCOVA

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	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: mm				
arithmetic mean (confidence interval 95%)	4.42 (2.6 to 6.2)	-0.11 (-1.9 to 1.7)	2.56 (0.7 to 4.4)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [9]
Method	ANCOVA

Notes:

[9] - Placebo vs 1.125% SYL1001: Dif 4.53 95%CI(2.0, 7.1) p=0.0007
Placebo vs 2.25% SYL1001: Dif 1.86 95%CI(-0.7, 4.4) p=0.1552
1.125% SYL1001 vs 2.25% SYL1001: Dif -2.67 95%CI(-5.3, -0.1) p=0.0427

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 post-treatment from day 0

End point values	Placebo	1.125% SYL1001	2.25% SYL1001	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	14	
Units: mm				
arithmetic mean (confidence interval 95%)	3.6 (2 to 5.2)	-0.17 (-1.7 to 1.4)	2.47 (0.6 to 4.3)	

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v 1.125% SYL1001 v 2.25% SYL1001
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 [10]
Method	ANCOVA

Notes:

[10] - Placebo vs 1.125% SYL1001: Dif 3.77 95%CI(1.5, 6.0) p=0.0014
Placebo vs 2.25% SYL1001: Dif 1.12 95%CI(-1.4, 3.6) p=0.3717
1.125% SYL1001 vs 2.25% SYL1001: Dif -2.64 95%CI(-5.1, -0.2) p=0.0337

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall periods	
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	1.125% SYL1001
Reporting group description:	
Patients assigned to 1.125% SYL1001 arm received 40 µL of 1.125% ophthalmic solution (0.45 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	
Reporting group title	2.25% SYL1001
Reporting group description:	
Patients assigned to any of the two SYL1001 arms received 40 µL of 2.25% ophthalmic solution (0.90 mg/eye/day) once daily in each eye over a period of 10 days via the ophthalmic route (ocular topical).	

Serious adverse events	Placebo	1.125% SYL1001	2.25% SYL1001
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (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	1.125% SYL1001	2.25% SYL1001
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	2 / 20 (10.00%)	2 / 20 (10.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2012	New site: Fundación Jiménez Díaz (IP: Ignacio Jiménez-Alfaro Morote)
03 May 2013	New site: Hospital Ramón y Cajal (IP Francisco José Muñoz Negrete)
05 December 2013	The dose of the investigational medicinal product administered to patients in the study was changed. It went from being 900 micrograms/40 microliters to 450 micrograms/40 microliters. Protocol version v2.0 dated on December 5, 2013 and the version of the Patient Information Sheet and Informed Consent v3.0 dated December 5, 2013 were generated.
03 March 2014	New sites: - Clínica Universitaria de Navarra (IP: Dr. Javier Moreno Montañés) - Instituto Clínico Quirúrgico de Oftalmología (IP: Dr. Juan Antonio Durán de la Colina)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported