Clinical trial results:
Dose- finding clinical trial with SYL040012 to evaluate the tolerability and effect on intraocular pressure in subjects with ocular hypertension or open-angle glaucoma

Summary

EudraCT number	2011-001849-33
Trial protocol	EE ES DE
Global end of trial date	30 April 2013

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	SYL040012_III

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1126-6866

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	26 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2013
Global end of trial reached?	Yes
Global end of trial date	30 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Tolerability in the ocular surface (cornea and conjunctiva) and effect on intraocular pressure after a daily dose of the investigational product during 14 days of treatment

Protection of trial subjects:

This clinical trial was conducted in compliance with Good Clinical Practice and the applicable national regulations to ensure that the rights and well-being of the participating subjects were protected consistent with the ethical principles that had their origin in the Declaration of Helsinki

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 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
Country: Number of subjects enrolled	Estonia: 37
Country: Number of subjects enrolled	Germany: 26
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	124
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 124 patients were screened from 18 July 2012 to 10 April 2013 in 11 centers in Spain, Germany and Estonia. A total of 35 patients were finally not included in the study.

Pre-assignment

Screening details:

- Signed informed consent
- Male and female subjects in good or fair general health
- Age ≥18 years
- Previous history or newly diagnosed IOP (≥21 mmHg)
- Normal result, or result typical for open-angle glaucoma (Visual field 24-2 or equivalent, OCT, BCVA, Schirmer test ≥0.5 (20/40), funduscopy)

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

Blinding implementation details:

Drug packaging applied 5- digit identifiers to the vials containing investigational product. The medication identifier was a random number to ensure there was no link between each number and the investigational product that it related to.
Both the labeling and the vials allowed to maintain the blinding throughout the study.
Treatment assignment was performed according to a randomization list blinded both for the sponsor and the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	SYL040012 80 µg

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 0.2% SYL040012 ophthalmic solution (80 µg) for 14 consecutive days

Arm type	Experimental
Investigational medicinal product name	SYL040012
Investigational medicinal product code	SYL040012
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

SYL040012 was administered to both eyes into the conjunctival sac once daily for 14 days. The investigational product was administered at the site by a designated site personnel staff. Investigational product administration took place at the same time every day, with an allowance of ± 1 hour with respect to the previous administration.

Arm title	SYL040012 300 µg

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 0.75% SYL040012 ophthalmic solution (300 µg) for 14 consecutive days

Arm type	Experimental

Investigational medicinal product name	SYL040012
Investigational medicinal product code	SYL040012
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

SYL040012 was administered to both eyes into the conjunctival sac once daily for 14 days. The investigational product was administered at the site by a designated site personnel staff. Investigational product administration took place at the same time every day, with an allowance of ± 1 hour with respect to the previous administration.

Arm title	SYL040012 900 µg

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 2.25% SYL040012 ophthalmic solution (900 µg) for 14 consecutive days

Arm type	Experimental
Investigational medicinal product name	SYL040012
Investigational medicinal product code	SYL040012
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

SYL040012 was administered to both eyes into the conjunctival sac once daily for 14 days. The investigational product was administered at the site by a designated site personnel staff. Investigational product administration took place at the same time every day, with an allowance of ± 1 hour with respect to the previous administration.

Arm title	Placebo

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of placebo ophthalmic solution for 14 consecutive days

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

Dosage and administration details:

Doses of placebo were administered to both eyes once daily for 14 days.

Number of subjects in period 1[1]	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg
Started	22	20	24
Completed	20	18	24
Not completed	2	2	0
Physician decision	-	1	-
Failure to return	-	1	-
Adverse event, non-fatal	1	-	-
IOP = 35 mmHg	1	-	-

Number of subjects in period 1[1]	Placebo
Started	23
Completed	22
Not completed	1
Physician decision	-
Failure to return	-
Adverse event, non-fatal	-
IOP = 35 mmHg	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: A total of 35 patients were finally not included in the study due to the following reasons: Inclusion/Exclusion criteria (32) and Withdrawal of consent (3).

Baseline characteristics

Reporting groups	
Reporting group title	SYL040012 80 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 0.2% SYL040012 ophthalmic solution (80 µg) for 14 consecutive days	

Reporting group title	SYL040012 300 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 0.75% SYL040012 ophthalmic solution (300 µg) for 14 consecutive days	
Reporting group title	SYL040012 900 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 2.25% SYL040012 ophthalmic solution (900 µg) for 14 consecutive days	
Reporting group title	Placebo
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of placebo ophthalmic solution for 14 consecutive days	

Reporting group values	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg
Number of subjects	22	20	24
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	55.7	58.2	56.8
standard deviation	± 12.65	± 12.99	± 15.71
Gender categorical Units: Subjects			
Female	15	12	16
Male	7	8	8
Race Units: Subjects			
White	22	20	24
Weight Units: Kg			
arithmetic mean	77.4	81.9	78.5
standard deviation	± 17.55	± 22.92	± 14.83
Height Units: cm			
arithmetic mean	168	166	164
standard deviation	± 9.71	± 11.38	± 10.11
BMI			
BMI=Body mass index			
Units: kg/m2			
arithmetic mean	27.2	29.3	29.2
standard deviation	± 5.13	± 5.81	± 5.25

Temperature			
Units: celsius temperature			
arithmetic mean	36.5	36.5	36.6
standard deviation	± 0.41	± 0.31	± 0.31

Reporting group values	Placebo	Total	
Number of subjects	23	89	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.9		
standard deviation	± 13.84	-	
Gender categorical			
Units: Subjects			
Female	17	60	
Male	6	29	
Race			
Units: Subjects			
White	23	89	
Weight			
Units: Kg			
arithmetic mean	75		
standard deviation	± 11.34	-	
Height			
Units: cm			
arithmetic mean	165		
standard deviation	± 9.44	-	
BMI			
BMI=Body mass index			
Units: kg/m2			
arithmetic mean	27.6		
standard deviation	± 4.24	-	
Temperature			
Units: celsius temperature			
arithmetic mean	36.5		
standard deviation	± 0.42	-	

End points

End points reporting groups

Reporting group title	SYL040012 80 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 0.2% SYL040012 ophthalmic solution (80 µg) for 14 consecutive days	

Reporting group title	SYL040012 300 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 0.75% SYL040012 ophthalmic solution (300 µg) for 14 consecutive days	
Reporting group title	SYL040012 900 µg
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of 2.25% SYL040012 ophthalmic solution (900 µg) for 14 consecutive days	
Reporting group title	Placebo
Reporting group description:	
Subjects received a daily administration of 1 drop in each of the eyes of placebo ophthalmic solution for 14 consecutive days	

Primary: Changes in IOP AUC

End point title	Changes in IOP AUC
End point description:	
IOP AUC=The intraocular pressure area under curve	
End point type	Primary
End point timeframe:	
The change from baseline in the area under the IOP curve on Day 14 was measured	

End point values	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	20	24	23
Units: AUC				
arithmetic mean (standard deviation)				
Right Eye	-36 (± 25.81)	-53 (± 29.29)	-21 (± 28.91)	-42 (± 31.02)
Left Eye	-45 (± 26.72)	-55 (± 28.04)	-30 (± 24.72)	-37 (± 32.57)

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	SYL040012 80 µg v SYL040012 300 µg v SYL040012 900 µg v Placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Mean differences (300µg vs 900µg)
Point estimate	-28.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.33
upper limit	-12.02

Notes:

[1] - All groups showed a reduction in the intraocular pressure at the end of the study. SYL040012 300µg showed the highest reduction in the symptoms when compared to baseline.
When treatment groups were compared, statistically significant differences were found in favor of SYL040012 300µg versus SYL040012 900µg : CI: -28.67 (LS Means: -45.33; -12.02)

Secondary: Change in the mean IOP

End point title	Change in the mean IOP

End point description:

End point type	Secondary

End point timeframe:

Change from baseline in the mean IOP at Day 14

End point values	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	20	24	23
Units: mmHg				
arithmetic mean (confidence interval 95%)	-2.642 (-3.251 to -2.033)	-3.534 (-4.176 to -2.893)	-1.687 (-2.243 to -1.131)	-2.618 (-3.198 to -2.038)

Attachments (see zip file)	IOP change/IOP.bmp

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	SYL040012 80 µg v SYL040012 300 µg v SYL040012 900 µg v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	repeated measures analysis mixed model

Notes:

[2] - Pb-80: 0.024 (-0.817,0.865) p=0.955
Pb-300: 0.916 (0.051,1.781) p=0.038
Pb-900: -0.931 (-1.734,-0.128) p=0.024
300-80: -0.892 (-1.777,-0.008) p=0.048

300-900: -1.847 (-2.696,-0.999) p=<.001
80-900: -0.955 (-1.779,-0.131) p=0.024

Secondary: Local tolerability: Cornea

End point title	Local tolerability: Cornea

End point description:

The tolerability variable was categorized as:
- Normal: No corneal or conjunctival alteration observed.
- Grade 1: Symptomatic or minimally symptomatic alterations observed, but which did not require intervention or interfere with function.
- Grade 2: Symptomatic alterations observed which interfered with the function but not with daily life, and required topical intervention.
- Grade 3: Symptomatic alterations observed which interfered with daily life, and required surgical intervention.

No dose limitation was found in any of the treatment groups. None of the patients reported any Grade 3 alterations in the corneal and conjunctival evaluation. All reactions were of grade 1 or normal except for one reaction of Grade 2 in the cornea of the right eye at Day 11 in one patient (4.2%) in the SYL040012 900 µg group. All treatments were well tolerated by all patients in any of the treatment groups

End point type	Secondary

End point timeframe:

Cornea: Corneal epithelium using fluorescein and Bengal pink or lissamine green dye. From day 1 to day 15

End point values	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	20	24	23
Units: number of subjects				
Day 1 - Grade 1 (right eye)	0	0	0	1
Day 1 - Grade 1 (left eye)	0	0	1	1
Day 3 - Grade 1 (right eye)	1	0	1	0
Day 3 - Grade 1 (left eye)	1	0	0	0
Day 4 - Grade 1 (right eye)	0	0	1	1
Day 4 - Grade 1 (left eye)	1	0	0	1
Day 5 - Grade 1 (left eye)	1	1	0	0
Day 6 - Grade 1 (right eye)	1	0	1	0
Day 6 - Grade 1 (left eye)	2	0	1	0
Day 7 - Grade 1 (right eye)	0	0	0	2
Day 7 - Grade 1 (left eye)	0	1	0	2
Day 8 - Grade 1 (right eye)	1	1	1	1
Day 8 - Grade 1 (left eye)	1	1	1	1
Day 9 - Grade 1 (right eye)	0	1	0	0
Day 10 - Grade 1 (right eye)	0	0	0	1
Day 10 - Grade 1 (left eye)	0	0	0	1
Day 11 - Grade 2 (right eye)	0	0	1	0
Day 11 - Grade 1 (left eye)	0	0	1	0
Day 12 - Grade 1 (right eye)	0	0	2	2
Day 12 - Grade 1 (left eye)	0	0	2	2
Day 13 - Grade 1 (right eye)	0	0	1	1
Day 13 - Grade 1 (left eye)	0	0	1	1
Day 14 - Grade 1 (right eye)	0	0	1	1

Day 14 - Grade 1 (left eye)	0	0	0	1
Day 15 - Grade 1 (right eye)	0	0	1	1
Day 15 - Grade 1 (left eye)	0	0	0	2

Statistical analyses

No statistical analyses for this end point

Secondary: Local tolerability: Conjunctiva

End point title	Local tolerability: Conjunctiva

End point description:

The tolerability variable was categorized as:
- Normal: No corneal or conjunctival alteration observed.
- Grade 1: Symptomatic or minimally symptomatic alterations observed, but which did not require intervention or interfere with function.
- Grade 2: Symptomatic alterations observed which interfered with the function but not with daily life, and required topical intervention.
- Grade 3: Symptomatic alterations observed which interfered with daily life, and required surgical intervention.

No dose limitation was found in any of the treatment groups. None of the patients reported any Grade 3 alterations in the corneal and conjunctival evaluation. All reactions were of grade 1 or normal except for one reaction of Grade 2 in the cornea of the right eye at Day 11 in one patient (4.2%) in the SYL040012 900 µg group. All treatments were well tolerated by all patients in any of the treatment groups

End point type	Secondary

End point timeframe:

Conjunctiva: Palpebral and bulbar conjunctival hyperemia. From day 1 to day 15

End point values	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	20	24	23
Units: number of subjects				
Day 1 - Grade 1 (right eye)	1	2	0	2
Day 1 - Grade 1 (left eye)	1	2	0	1
Day 2 - Grade 1 (right eye)	0	0	1	0
Day 3 - Grade 1 (right eye)	1	0	1	1
Day 3 - Grade 1 (left eye)	2	0	1	1
Day 4 - Grade 1 (right eye)	0	0	0	1
Day 4 - Grade 1 (left eye)	1	0	0	1
Day 5 - Grade 1 (left eye)	1	0	0	0
Day 6 - Grade 1 (right eye)	0	0	1	0
Day 6 - Grade 1 (left eye)	1	1	1	0
Day 7 - Grade 1 (right eye)	0	1	0	0
Day 7 - Grade 1 (left eye)	0	1	0	0
Day 8 - Grade 1 (right eye)	0	1	0	1
Day 8 - Grade 1 (left eye)	0	1	0	1
Day 9 - Grade 1 (right eye)	0	2	0	0
Day 9 - Grade 1 (left eye)	0	1	0	0
Day 10 - Grade 1 (right eye)	1	1	0	1

Day 10 - Grade 1 (left eye)	1	1	0	1
Day 11 - Grade 1 (right eye)	1	1	0	0
Day 11 - Grade 1 (left eye)	1	2	0	0
Day 12 - Grade 1 (right eye)	0	0	2	1
Day 12 - Grade 1 (left eye)	0	0	2	1
Day 13 - Grade 1 (right eye)	0	0	1	0
Day 13 - Grade 1 (left eye)	1	0	1	0
Day 14 - Grade 1 (left eye)	0	0	1	1

Statistical analyses

No statistical analyses for this end point

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	SYL040012 80 µg
Reporting group description:	
Doses of 80 µg SYL040012 were administered to both eyes once daily for 14 days.	
Reporting group title	SYL040012 300 µg
Reporting group description:	
Doses of 300 µg SYL040012 were administered to both eyes once daily for 14 days.	
Reporting group title	SYL040012 900 µg
Reporting group description:	
Doses of 900 µg SYL040012 were administered to both eyes once daily for 14 days.	
Reporting group title	Placebo
Reporting group description:	
Doses of placebo were administered to both eyes once daily for 14 days.	

Serious adverse events	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SYL040012 80 µg	SYL040012 300 µg	SYL040012 900 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 22 (45.45%)	9 / 20 (45.00%)	12 / 24 (50.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hypertensive crisis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Oropharyngeal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Investigations			
Catheterisation cardiac			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Eye burns			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Foreign body in eye			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	1 / 20 (5.00%)	5 / 24 (20.83%)
occurrences (all)	4	3	6
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Conjunctival hyperaemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	2 / 24 (8.33%)
occurrences (all)	4	0	2
Conjunctival oedema			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dry eye			

subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Eye pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	4
Eye pruritus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ocular discomfort			
subjects affected / exposed	0 / 22 (0.00%)	3 / 20 (15.00%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Punctate keratitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	2	0	4
Vision blurred			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Oral herpes			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Hypertensive crisis			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Investigations			
Catheterisation cardiac			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Eye burns			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Foreign body in eye			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Conjunctival hyperaemia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	5		
Conjunctival oedema			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Eye pruritus			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Ocular discomfort			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Punctate keratitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	4		
Vision blurred			

subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2012	There was a non-substantial protocol amendment which included the following modifications: • Modification of the inclusion criteria no. 5 • Ocular fundus / fundus photography done on Day 15 • Subjective baseline visual analogue scale assessment • Modification of the exclusion criteria no. 17 • Dye to be used in corneal examination

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported