



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 Grisolia 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 μ g |

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 0.2% SYL040012 ophthalmic solution (80 μ g) 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 μ g |
|------------------|-----------------------|

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 0.75% SYL040012 ophthalmic solution (300 μ g) 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 μ g |
|------------------|-----------------------|

Arm description:

Subjects received a daily administration of 1 drop in each of the eyes of 2.25% SYL040012 ophthalmic solution (900 μ g) 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 μ g | SYL040012 300 μ g | SYL040012 900 μ g |
|---|----------------------|-----------------------|-----------------------|
| 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 standard deviation | 55.7 ± 12.65 | 58.2 ± 12.99 | 56.8 ± 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 standard deviation | 77.4 ± 17.55 | 81.9 ± 22.92 | 78.5 ± 14.83 |
| Height Units: cm arithmetic mean standard deviation | 168 ± 9.71 | 166 ± 11.38 | 164 ± 10.11 |
| BMI | | | |
| BMI=Body mass index | | | |
| Units: kg/m ² arithmetic mean standard deviation | 27.2 ± 5.13 | 29.3 ± 5.81 | 29.2 ± 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 occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 20 (5.00%) 1 | 0 / 24 (0.00%) 0 |
| Investigations Catheterisation cardiac subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 20 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Injury, poisoning and procedural complications Eye burns subjects affected / exposed occurrences (all) Foreign body in eye subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 | 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 | 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 |
| Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 20 (5.00%) 1 | 0 / 24 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 4 | 1 / 20 (5.00%) 3 | 5 / 24 (20.83%) 6 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 20 (5.00%) 1 | 0 / 24 (0.00%) 0 |
| Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) Conjunctival hyperaemia subjects affected / exposed occurrences (all) Conjunctival oedema subjects affected / exposed occurrences (all) Dry eye | 0 / 22 (0.00%) 0 2 / 22 (9.09%) 4 0 / 22 (0.00%) 0 | 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 | 0 / 24 (0.00%) 0 2 / 24 (8.33%) 2 0 / 24 (0.00%) 0 |

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

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 2 / 23 (8.70%) 2 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 1 / 23 (4.35%) 1 2 / 23 (8.70%) 2 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 | | |
| Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 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 | <p>There was a non-substantial protocol amendment which included the following modifications:</p> <ul style="list-style-type: none">• 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