



## 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 Grisolia nº 2, Tres Cantos, Madrid, Spain, 28760 |
| Public contact               | Head of Regulatory Affairs & QP, Sylentis S.A.U.<br>, +34 918047667, info@sylentis.com   |
| Scientific contact           | Head of Regulatory Affairs & QP, Sylentis S.A.U.<br>, +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     |
| <b>Arm title</b>             | 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

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | 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)

|                                                                                                                                                                                                                               |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| <b>Arm title</b>                                                                                                                                                                                                              | 2.25% SYL1001       |
| Arm description:<br>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)

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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:<br>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:<br>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:<br>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<br>Units: Subjects                               |                         |                         |                         |
| Adults (18-64 years)                                             | 17                      | 15                      | 13                      |
| From 65-84 years                                                 | 3                       | 5                       | 7                       |
| Age continuous<br>Units: years<br>median<br>full range (min-max) | 40.39<br>23.56 to 75.38 | 45.83<br>27.36 to 76.35 | 60.67<br>27.89 to 78.23 |
| Gender categorical<br>Units: Subjects                            |                         |                         |                         |
| Female                                                           | 15                      | 17                      | 18                      |
| Male                                                             | 5                       | 3                       | 2                       |
| Hyperemia - Right eye<br>Units: Subjects                         |                         |                         |                         |
| Normal                                                           | 11                      | 7                       | 15                      |
| Abnormal                                                         | 9                       | 13                      | 5                       |
| Hyperemia - Left eye<br>Units: Subjects                          |                         |                         |                         |
| Normal                                                           | 12                      | 8                       | 15                      |
| Abnormal                                                         | 8                       | 12                      | 5                       |
| Corneal fluorescein staining - Right eye<br>Units: Subjects      |                         |                         |                         |
| Oxford I                                                         | 14                      | 12                      | 13                      |
| Oxford II                                                        | 5                       | 7                       | 6                       |
| Oxford III                                                       | 1                       | 1                       | 1                       |
| Corneal fluorescein staining - Left eye<br>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 |
| <b>Reporting group values</b>   |            |            |             |
|                                 | 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<br>median<br>full range (min-max)                                | - |  |  |
| Visual acuity - Right eye<br>Units: points<br>median<br>full range (min-max) | - |  |  |
| Visual acuity - Left eye<br>Units: units<br>median<br>full range (min-max)   | - |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                               |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                         | Placebo            |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>OSDI=Ocular surface disease index             |                               |
| End point type                                                          | Primary                       |
| End point timeframe:<br>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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 |                                    |

|                                           |                        |                       |                        |  |
|-------------------------------------------|------------------------|-----------------------|------------------------|--|
| <b>End point values</b>                   | 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) |  |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Attachments (see zip file)</b> | OSDI score/OSDI score (PP).bmp |
|-----------------------------------|--------------------------------|

## Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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) |  |

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Attachments (see zip file)</b> | VAS score/VAS score pre-adm.bmp |
|-----------------------------------|---------------------------------|

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>                  |
| 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) |  |

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Attachments (see zip file)</b> | VAS score/VAS score post-adm.bmp |
|-----------------------------------|----------------------------------|

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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:<br>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:<br>at day 10 post-treatment from day 1                                                                                                                                                                                                                                                                      |                                                       |

|                                           |                    |                      |                      |  |
|-------------------------------------------|--------------------|----------------------|----------------------|--|
| <b>End point values</b>                   | 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) |  |

|                                   |                                        |
|-----------------------------------|----------------------------------------|
| <b>Attachments (see zip file)</b> | VAS score/VAS score post-adm (imp).bmp |
|-----------------------------------|----------------------------------------|

### Statistical analyses

|                                   |                                          |
|-----------------------------------|------------------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[2]</sup> |
| 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) |  |

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Attachments (see zip file)</b> | VAS score/VAS score pre-adm (PP).bmp |
|-----------------------------------|--------------------------------------|

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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:<br>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:<br>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) |  |

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

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup>                   |
| 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

| <b>End point values</b>                   | 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) |  |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Attachments (see zip file)</b> | VAS score/VAS score by day.bmp |
|-----------------------------------|--------------------------------|

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>                  |
| 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

|                             |                 |                 |                 |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| <b>End point values</b>     | 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>                  |
| 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[6]</sup>                  |
| 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 <sup>[7]</sup>                  |
| 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[8]</sup>                  |
| 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

|                                   |                                          |
|-----------------------------------|------------------------------------------|
| <b>Statistical analysis title</b> | 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%<br>SYL1001 | 2.25%<br>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                          |               |

| <b>End point values</b>     | Placebo         | 1.125%<br>SYL1001 | 2.25%<br>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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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                          |                    |

| <b>End point values</b>     | Placebo         | 1.125%<br>SYL1001 | 2.25%<br>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



|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 |                    |

| <b>End point values</b>                   | 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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   |                |

| <b>End point values</b>                   | 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

|                                   |                                          |
|-----------------------------------|------------------------------------------|
| <b>Statistical analysis title</b> | 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 |                |

| <b>End point values</b>                   | 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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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   |                     |

| <b>End point values</b>                   | 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

|                                   |                                          |
|-----------------------------------|------------------------------------------|
| <b>Statistical analysis title</b> | 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:<br>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

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[9]</sup>                   |
| 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:<br>at day 10 post-treatment from day 0 |                                |

| <b>End point values</b>                   | 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

| <b>Statistical analysis title</b>       | 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 <sup>[10]</sup>                 |
| 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<br>subjects affected / exposed<br>occurrences (all)                                                          | 3 / 20 (15.00%)<br>3 | 0 / 20 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                           | 1 / 20 (5.00%)<br>1  | 0 / 20 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1 |
| General disorders and administration<br>site conditions<br>Malaise<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1 |
| Eye disorders<br>Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 20 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1 |
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)                                                       | 0 / 20 (0.00%)<br>0  | 2 / 20 (10.00%)<br>2 | 0 / 20 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 20 (10.00%)<br>2 | 0 / 20 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0 |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 20 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  | 1 / 20 (5.00%)<br>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.<br>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:<br>- Clínica Universitaria de Navarra (IP: Dr. Javier Moreno Montañés)<br>- Instituto Clínico Quirúrgico de Oftalmología (IP: Dr. Juan Antonio Durán de la Colina)                                                                                                                                                                                |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported