Clinical trial results:
A double-masked study of SYL1001 in patients with moderate to severe dry eye disease (DED)

Summary

EudraCT number	2016-003903-79
Trial protocol	DE ES PT EE SK IT
Global end of trial date	16 November 2018

Results information

Result version number	v1 (current)
This version publication date	02 December 2019
First version publication date	02 December 2019

Trial information

Trial identification

Sponsor protocol code	SYL1001_IV

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sylentis SAU – Pharma Mar Group
Sponsor organisation address	Parque Tecnológico de Madrid C/Santiago Grisolía nº 2 Tres Cantos 28760, Madrid, Spain,
Public contact	Regulatory Affairs, Sylentis SAU, +34 91806 31 88, vruz@sylentis.com
Scientific contact	Regulatory Affairs, Sylentis SAU, +34 91806 31 88, vruz@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	16 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2018
Global end of trial reached?	Yes
Global end of trial date	16 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives:
1. Change from Baseline in Visual Analogue Scale (VAS) scores for eye discomfort/pain after 28 days of treatment.
2. Change from Baseline in Corneal Fluorescein Staining (CFS) total scores obtained on the Oxford scale after 28 days of treatment.
3. Change from Baseline in conjunctival hyperemia scores based on the McMonnies scale after 28 days of treatment.

Protection of trial subjects:

This study was conducted in accordance with the protocol, the ICH guidelines and guidelines for Good Clinical Practice (GCP), with the Declaration of Helsinki (revised version, Fortaleza, October 2013) and the local laws and guidelines of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2017
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	Portugal: 4
Country: Number of subjects enrolled	Slovakia: 47
Country: Number of subjects enrolled	Spain: 105
Country: Number of subjects enrolled	Estonia: 69
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Italy: 28
Worldwide total number of subjects	289
EEA total number of subjects	289

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	186
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 289 patients, 143 in the SYL1001 and 146 in the vehicle group were randomized and received treatment at 15 clinical sites in Spain, 2 clinical sites in Portugal, 8 clinical sites in Germany, 3 clinical sites in Estonia, 4 clinical sites in Italy and 7 clinical sites in Slovakia.

Pre-assignment

Screening details:

Once suitability for the study was verified, patients entered a 7-day run-in period. They self-administrated the vehicle ophthalmic solution once a day at 09:00am ± 1 hour. During the run-in period, patients noted all instillation times into a diary. Administration of artificial tears at least ± 1 hour from vehicle administration, max 4 drops/day

Pre-assignment period milestones

Number of subjects started	289
Number of subjects completed	289

Period 1

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

Blinding implementation details:

A computer-generated randomization schedule using a block design was used to assign subjects to the two treatment arms. The vehicle and SYL1001 ophthalmic solution were supplied in a way in that they were indistinguishable from each other, in order to maintain the masking of the clinical trial. The Sponsor provided a kit containing the single-dose plastic containers of the assigned treatment for each patient. Neither the research team or patient knew which treatment they had been assigned.

Arms

Are arms mutually exclusive?	Yes
Arm title	SYL1001

Arm description:

11.25 mg/mL SYL1001 ophthalmic solution, one drop per eye per day for 28 consecutive days

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

Dosage and administration details:

11.25 mg/mL, one drop per eye per day for 28 consecutive days

Arm title	Vehicle Solution

Arm description:

Buffer saline solution 0.97%, one drop per eye each day for 28 consecutive days

Arm type	Placebo

Investigational medicinal product name	buffer saline solution 0.97%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop per eye each day for 28 consecutive days

Number of subjects in period 1	SYL1001	Vehicle Solution
Started	143	146
Completed	132	139
Not completed	11	7
At specific request of the sponsor	1	1
Onset of any non-inclusion criteria	1	-
Compliance less than indicated in the protocol	4	-
Lost to follow-up	-	1
Intercurrent disease or intolerable AE	2	2
Protocol deviation	3	3

Baseline characteristics

Reporting groups	
Reporting group title	SYL1001
Reporting group description:	
11.25 mg/mL SYL1001 ophthalmic solution, one drop per eye per day for 28 consecutive days	
Reporting group title	Vehicle Solution
Reporting group description:	
Buffer saline solution 0.97%, one drop per eye each day for 28 consecutive days	

Reporting group values	SYL1001	Vehicle Solution	Total
Number of subjects	143	146	289
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	90	96	186
From 65-84 years	53	50	103
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	118	125	243
Male	25	21	46
Ethnic Group Units: Subjects			
Asian	0	0	0
Black	0	1	1
Caucasian	125	122	247
Other	0	4	4
Not provided as per local laws	18	19	37

End points

End points reporting groups

Reporting group title	SYL1001
Reporting group description:	
11.25 mg/mL SYL1001 ophthalmic solution, one drop per eye per day for 28 consecutive days	
Reporting group title	Vehicle Solution
Reporting group description:	
Buffer saline solution 0.97%, one drop per eye each day for 28 consecutive days	

Primary: Primary efficacy endpoint: Score for eye discomfort/pain

End point title	Primary efficacy endpoint: Score for eye discomfort/pain

End point description:

Change from Baseline in Visual Analogue Scale (VAS) score for eye discomfort/pain after 28 days of treatment, which was defined as VAS at analysis visit 3 – VAS at Baseline.
Eye discomfort/pain was analyzed from the scores recorded in the eCRF by the investigator. This score represents the distance (mm) from 0 in the corresponding eye discomfort/pain visual analogue scale and ranges from 0 to 100. Higher scores in the VAS described worst severity.

End point type	Primary
End point timeframe:	
Baseline and Day 28	

End point values	SYL1001	Vehicle Solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	146		
Units: unit(s)				
arithmetic mean (standard deviation)				
Absolute change from baseline number	-16.10 (± 21.31)	-16.58 (± 21.62)		

Statistical analyses

Statistical analysis title	Statistical analysis 1 for Clinical Efficacy

Statistical analysis description:

Change from Baseline in Visual Analogue Scale (VAS) score for eye discomfort/pain after 28 days of treatment.

Comparison groups	SYL1001 v Vehicle Solution

Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.926
Method	ANCOVA

Primary: Primary efficacy endpoint: Corneal Fluorescein Staining

End point title	Primary efficacy endpoint: Corneal Fluorescein Staining

End point description:

Change from Baseline in Corneal Fluorescein Staining (CFS) after 28 days of treatment. The Oxford scale ranges from 0 to 5 (0 = no staining, 5= severe) with 0.5 points increments. The eye was divided into five zones: central, nasal, temporal, superior and inferior. Each zone was scored separately and recorded in the CRF. The Total score CFS obtained on the Oxford scale was defined as the sum of the five zones scores (0 to 25). Change was calculated as the CFS at analysis visit 3 – CFS at Baseline. Higher scores in the Oxford scale described worst severity.

End point type	Primary

End point timeframe:

Baseline and Day 28

End point values	SYL1001	Vehicle Solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	146		
Units: unit(s)				
arithmetic mean (standard deviation)				
Absolute change from baseline number	-2.37 (± 2.97)	-1.71 (± 3.00)		

Statistical analyses

Statistical analysis title	Statistical analysis 2 for Clinical Efficacy

Statistical analysis description:

Change from Baseline in Corneal Fluorescein Staining (CFS) after 28 days of treatment

Comparison groups	SYL1001 v Vehicle Solution
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.208
Method	ANCOVA

Primary: Primary efficacy endpoint: Conjunctival hyperemia score

End point title	Primary efficacy endpoint: Conjunctival hyperemia score

End point description:

Change from Baseline in conjunctival hyperemia score based on the McMonnies scale after 28 days of

treatment, which was defined as McMonnies at analysis visit 3 - McMonnies at Baseline. The McMonnies scale ranges from 0 to 5. Conjunctival hyperemia was analysed from the scores recorded in the eCRF by the investigator. Higher scores in the McMonnies scale described worst severity.

End point type	Primary

End point timeframe:

Baseline and Day 28

End point values	SYL1001	Vehicle Solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	146		
Units: unit(s)				
arithmetic mean (standard deviation)				
Absolute change from baseline number	-0.51 (± 0.88)	-0.44 (± 0.90)		

Statistical analyses

Statistical analysis title	Statistical analysis 3 for Clinical Efficacy

Statistical analysis description:

Change from Baseline in conjunctival hyperemia score based on the McMonnies scale after 28 days of treatment

Comparison groups	SYL1001 v Vehicle Solution
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.451
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days

Adverse event reporting additional description:

5 patients had serious non-ocular AEs reported, 1 in the SYL1001 group & 4 in the vehicle group; none was related to treatment.
9 patients had 13 treatment related ocular AEs, 6 in the SYL1001 group had 8 related ocular AEs and 3 in the vehicle groups had 5 related ocular AE's. 1 patient in the SYL1001 group reported 1 related non-ocular AE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	SYL1001

Reporting group description:

11.25 mg/mL SYL1001 ophthalmic solution, one drop per eye per day for 28 consecutive days

Reporting group title	Vehicle Solution

Reporting group description:

Buffer saline solution 0.97%, one drop per eye each day for 28 consecutive days

Serious adverse events	SYL1001	Vehicle Solution	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 143 (0.70%)	4 / 146 (2.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			

subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SYL1001	Vehicle Solution	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 143 (25.87%)	39 / 146 (26.71%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cyst removal			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 143 (1.40%)	1 / 146 (0.68%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	3	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 143 (0.70%)	1 / 146 (0.68%)	
occurrences (all)	1	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Blood creatine increased			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Eosinophil count increased			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Platelet count abnormal			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Scan myocardial perfusion			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Eye burns			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	

Snake bite			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Distichiasis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 143 (2.10%)	2 / 146 (1.37%)	
occurrences (all)	5	2	
Dizziness			
subjects affected / exposed	1 / 143 (0.70%)	1 / 146 (0.68%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Eye disorders			
Eye irritation			
subjects affected / exposed	3 / 143 (2.10%)	2 / 146 (1.37%)	
occurrences (all)	3	3	
Photophobia			
subjects affected / exposed	2 / 143 (1.40%)	0 / 146 (0.00%)	
occurrences (all)	2	0	
Blepharitis allergic			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	3 / 143 (2.10%)	0 / 146 (0.00%)	
occurrences (all)	5	0	
Eye pain			

subjects affected / exposed	2 / 143 (1.40%)	4 / 146 (2.74%)		
occurrences (all)	2	4		
Vision blurred				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	1		
Dry eye				
subjects affected / exposed	3 / 143 (2.10%)	1 / 146 (0.68%)		
occurrences (all)	4	1		
Ocular toxicity				
subjects affected / exposed	2 / 143 (1.40%)	0 / 146 (0.00%)		
occurrences (all)	2	0		
Blindness				
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)		
occurrences (all)	1	0		
Eyelids pruritus				
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)		
occurrences (all)	1	0		
Lacrimation increased				
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)		
occurrences (all)	1	0		
Chalazion				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	1		
Corneal erosion				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	2		
Ectropion				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	1		
Eyelid cyst				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	1		
Foreign body sensation in eyes				
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)		
occurrences (all)	0	1		
Ocular discomfort				

subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Punctate keratitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Odynophagia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	0 / 143 (0.00%)	2 / 146 (1.37%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Joint effusion			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 143 (2.10%)	4 / 146 (2.74%)	
occurrences (all)	3	4	
Influenza			
subjects affected / exposed	1 / 143 (0.70%)	2 / 146 (1.37%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	2	
Pharyngitis			

subjects affected / exposed	0 / 143 (0.00%)	2 / 146 (1.37%)	
occurrences (all)	0	2	
Tooth infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	Addition of a Clinical Global Impression Questionnaire for both patient and Clinician at Day 28. Addition of Impression Cytology procedure at Day 0 and Day 28. Update of the inclusion criterion #10 Previous wording: "Corrected visual acuity ≥0.7 logMAR (20/100 Snellen or 50 ETDRS) in both eyes". New wording: "Corrected visual acuity ≤ 0.7 logMAR (≥20/100 Snellen or ≥50 ETDRS) in both eyes" Update of the paragraph related to inclusion criteria for VAS. Previous wording: "Assessment of inclusion/non-inclusion criteria will be performed both at the Screening Visit (V0) and at the Baseline visit (V1). All inclusion criteria must be met in the eye with the highest VAS scoring. VAS must be ≥ 20 for the fellow eye. The eye with the highest VAS scoring at the Screening Visit (V0) is not necessarily the same eye with the highest VAS scoring at the Baseline Visit. […]" New wording: "Assessment of inclusion/non-inclusion criteria will be performed both at the Screening Visit (V0) and at the Baseline visit (V1). Since the allocated treatment will be administered in both eyes, a minimum level of 20 in the VAS scale for pain/discomfort is required in the two eyes. All inclusion criteria must be met in the eye with the highest VAS scoring. VAS must be ≥ 20 for the fellow eye. The eye with the highest VAS scoring at the Screening Visit (V0) is not necessarily the same eye with the highest VAS scoring at the Baseline Visit. […]" Update of the non-inclusion criterion #2 Previous wording: "[…] and documented use of condoms". New wording: "[…] and documented use of condoms" Update of the non-inclusion criterion #9 Previous wording: "Use of contact lenses or punctual plugs during the treatment and the previous 7 days (prior to treatment initiation)." New wording: "Use of contact lenses or presence of punctual plugs during the treatment and the previous 7 days (prior to treatment initiation)."

06 June 2017	Update of the non-inclusion criterion #11 Previous wording: "Previous refractive surgery, cornea transplant. Meibomian gland dysfunction or history of lid malposition (ectropion, entropion, ptosis), that may affect accurate assessment of the disease and/or mask the effects of the drug New wording: " Previous refractive surgery, cornea transplant. Meibomian gland dysfunction or history of lid malposition (ectropion, entropion, ptosis), history of recurrent corneal herpes or history of recurrent corneal erosion or neurotrophic keratopathy that may affect accurate assessment of the disease and/or mask the effects of the drug" Paragraph 5.2. Randomization is more consistent: "Patients who meet all of the inclusion and none of the non-inclusion criteria at the Baseline visit will be randomized. Treatments will be allocated following a pre-established randomization list using a random design by blocks created by Linical Co. Ltd. The team ins charge of the randomization is located at a separate office from the main reporting team in order to preserve the masking of the investigational product. Numbers will consist of 5-digit identifiers which will act as both Subject Randomization Number and Medication Identifier. Drug packaging (Idifarma) will apply these 5-digit identifiers to the vials containing the investigational products. Once the investigator has confirmed that a subject is eligible for randomization, the eCRF will assign the next randomization number available at the site and this number medication will be used throughout the entire treatment period.
06 June 2017	Drug packaging will retain a list of the mapping of 5-digit identifiers to investigational product which will be supplied to the reporting statistician only at the time of full study unmasking, post database lock, in order to determine the medication actually received. The information on this list will also be provided to the designated research personnel of each site in a sealed, tamper-proof format such that emergency unmasking of the contents of a single vial only can be performed if required." Update of protocol titles 4.1 and 4.2. Previous wording: "4.1. Primary outcomes" & "4.2. Secondary outcomes" New wording: "4.1. Primary outcomes/objectives"& "4.2. Secondary outcomes/objectives" 7.4.1 Labelling distribution and storage Name of manufacturer of artificial tears was changed from "Theradis" to "Idifarma" 8.1 Detailed Study Plan The order of procedures has been updated 8.3.3 Ocular tests – IOP Previous wording: "The IOP measurement will be performed in both eyes between 9 a.m. and 12 p.m by contact tonometry." New wording: "The IOP measurement will be performed in both eyes at the same time (± 1 h) at every visit between 9 a.m. and 12 p.m. by contact tonometry." 10.2.8 Notifications of AEs Update of the email address to be used for notifications of AEs 12.4 Confidentiality of data; 14.1 Source documents; 14.3 Monitoring In these sections, addition that the direct access to the data by Monitors (access direct conditioned to the compliance of certain rules) and by Regulatory Authorities as well as Ethics Committee remains through the investigator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: