Clinical trial results:
A Phase II, multicentre, randomised, placebo-controlled, double-masked trial of RP101 ophthalmic formulation versus vehicle in post-menopausal women with moderate to severe dry eye syndrome

Summary

EudraCT number	2017-005160-18
Trial protocol	AT HU DE
Global end of trial date	18 November 2019

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	RP101-200

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03821415
WHO universal trial number (UTN)	-
Other trial identifiers	CRO code number: CRO-17-132

Notes:

Sponsors

Sponsor organisation name	Redwood Pharma AB
Sponsor organisation address	Ringvägen 100E, 9th Floor, Stockholm, Sweden, SE-118 60
Public contact	Redwood Pharma AB, Sponsor representative, Redwood Pharma AB, 0046 (08)55934737, martin.vidaeus@redwoodpharma.com
Scientific contact	Redwood Pharma AB, Sponsor representative, Redwood Pharma AB, 0046 (08)55934737, martin.vidaeus@redwoodpharma.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	24 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to establish the effective dose/dose regimen of RP101 in post-menopausal women with moderate to severe dry eye syndrome applying RP101 ophthalmic sterile solution or matching placebo (vehicle) once (q.d.) or twice a day (b.i.d.) for 3 months

Protection of trial subjects:

The indication proposed for RP101 is dry eye syndrome of moderate-to-severe intensity in postmenopausal women. Therefore, the population selected for the present study was composed of postmenopausal women for at least 3 years presenting with symptoms specific for dry eye syndrome of moderate-to-severe intensity. Patients presenting with severe Meibomian gland dysfunction were excluded due to its potential interference, since a Meibomian gland dysfunction of severe intensity would lead to underestimate the RP101 effect.
The participants in the study could receive benefit from the study treatment because they could experience a relief of dry eye symptoms during the study. Also the patients randomly allocated to the control arm, who received the vehicle (RP101 without the active substance), could receive some benefit from IntelliGel (placebo; vehicle) which was expected to have lubricant properties due to its rheological behaviour.
Safety of the subjects was monitored throughout the study.

Background therapy:

All the previous ocular therapies for moderate/severe dry eye symptom up to screening were discontinued. At study start, all patients used the same topical lubricant for 14 consecutive days (run-in period) in order to start at baseline at homogeneous conditions. During the run-in, all the subjects used the same ocular product (Oculotect®) in order to standardise baseline conditions.

After the run-in, the subjects were randomised and started the allocated study treatment.
In case of need during the study treatment, the patients could instil Larmabak®, artificial tears, as rescue medication in addition to the study treatment.

Evidence for comparator:

In the present study, 2 strengths of RP101 were investigated: 0.1% and 0.05%. IntelliGel® (RP101 vehicle) was selected as the placebo (vehicle) in this study because of its unique properties and to mask the study.

Actual start date of recruitment	18 January 2019
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	Austria: 8
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 89

Worldwide total number of subjects	104
EEA total number of subjects	104

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)	63
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 18JAN2019 to 28JUN2019
Territories were: Vienna, Austria; München, Germany; Greifswald, Germany; Mainz, Germany; Létavértes, Hungary; Budapest, Hungary; Székesfehérvár Berényi, Hungary

Pre-assignment

Screening details:

During screening, inclusion and exclusion criteria were checked and only eligible patients enrolled in the study. At study start, all patients used the same topical lubricant for 14 consecutive days (run-in period) in order to start at baseline at homogeneous conditions. All screened patients are listed on the screen log.

Pre-assignment period milestones

Number of subjects started	104
Number of subjects completed	104

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, Data analyst, Carer, Assessor

Blinding implementation details:

Clinical staff, CRO, CRAs, Sponsor, patients were blinded. Blinding was open by data managers only after DB lock. Breaking of an individual randomisation code by the investigator during the study was allowed only when knowledge of the code was essential for the subject's health.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group 1

Arm description:

Active investigational product (T1) twice a day

Arm type	Experimental
Investigational medicinal product name	RP101 0.05%, 17-β-oestradiol-3-phosphate ophthalmic sterile solution
Investigational medicinal product code	T1
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (28 µL) according to the treatment group and dose regimen was instilled into each eye twice a day (b.i.d.), approximately every 12 h (08:30 ± 1.5 h and 20:30 ± 1.5 h), for 90±3 consecutive days.

Arm title	Treatment group 2

Arm description:

Active investigational product (T2) and placebo

Arm type	Experimental

Investigational medicinal product name	RP101 0.1%, 17-β-oestradiol-3-phosphate ophthalmic sterile solution
Investigational medicinal product code	T2
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (28 µL) of T2 was instilled into each eye once a day at approximately 8:30 ± 1.5 h for 90±3 consecutive days.

Investigational medicinal product name	RP101 matching placebo, ophthalmic sterile solution
Investigational medicinal product code	P
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (28 µL) of P was instilled into each eye once a day at 20:30 ± 1.5 h for 90±3 consecutive days.

Arm title	Treatment group 3

Arm description:

Active investigational product twice a day

Arm type	Experimental
Investigational medicinal product name	RP101 0.1%, 17-β-oestradiol-3-phosphate ophthalmic sterile solution
Investigational medicinal product code	T2
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (28 µL) of T2 was instilled into each eye twice a day (b.i.d.), approximately every 12 h (08:30 ± 1.5 h and 20:30 ± 1.5 h), for 90±3 consecutive days.

Arm title	Treatment group 4

Arm description:

Placebo twice a day

Arm type	Placebo
Investigational medicinal product name	RP101 matching placebo, ophthalmic sterile solution
Investigational medicinal product code	P
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop (28 µL) of P was instilled into each eye twice a day (b.i.d.), approximately every 12 h (08:30 ± 1.5 h and 20:30 ± 1.5 h), for 90±3 consecutive days

Number of subjects in period 1	Treatment group 1	Treatment group 2	Treatment group 3
Started	27	25	26
Completed	20	22	13
Not completed	7	3	13
Consent withdrawn by subject	1	1	3
Adverse event, non-fatal	6	2	10

Number of subjects in period 1	Treatment group 4
Started	26
Completed	22
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	104	104	
Age categorical			
Age range of the women in the study was 39-83 years			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	63	63	
From 65-84 years	41	41	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	62.9		
standard deviation	± 8.7	-	
Gender categorical			
Only post-menopausal women were included in the study, according to the protocol requirements			
Units: Subjects			
Female	104	104	
Male	0	0	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

aAl randomised subjects who received at least one dose of the investigational product and had at least one post-randomisation assessment of the primary efficacy data. This analysis set was used for the primary efficacy analysis. This analysis set corresponded also to the Intent-To-Treat set.

Subject analysis set title	PP set
Subject analysis set type	Per protocol

Subject analysis set description:

All randomised subjects who fulfilled the study protocol requirements in terms of investigational product administration and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the sensitivity analyses;

Subject analysis set title	Saftey set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of investigational product. This analysis set was used for the safety analyses

Subject analysis set title	PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK Set (only for the PK sub-study): all randomised subjects who had evaluable PK data readouts. This analysis set was used for the PK analysis;

Reporting group values	Full Analysis Set	PP set	Saftey set
Number of subjects	104	67	104
Age categorical			
Age range of the women in the study was 39-83 years			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	62.9	61.7	62.9
standard deviation	± 8.7	± 8.5	± 8.7
Gender categorical			
Only post-menopausal women were included in the study, according to the protocol requirements			
Units: Subjects			
Female	104	67	104
Male	0	0	0

Reporting group values	PK set		
Number of subjects	71		
Age categorical			
Age range of the women in the study was 39-83 years			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	61.2		
standard deviation	± 8.4		

Gender categorical			
Only post-menopausal women were included in the study, according to the protocol requirements			
Units: Subjects			
Female	71		
Male	0		

End points

End points reporting groups

Reporting group title	Treatment group 1
Reporting group description:	
Active investigational product (T1) twice a day	
Reporting group title	Treatment group 2
Reporting group description:	
Active investigational product (T2) and placebo	
Reporting group title	Treatment group 3
Reporting group description:	
Active investigational product twice a day	
Reporting group title	Treatment group 4
Reporting group description:	
Placebo twice a day	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
aAl randomised subjects who received at least one dose of the investigational product and had at least one post-randomisation assessment of the primary efficacy data. This analysis set was used for the primary efficacy analysis. This analysis set corresponded also to the Intent-To-Treat set.	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomised subjects who fulfilled the study protocol requirements in terms of investigational product administration and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for the sensitivity analyses;	
Subject analysis set title	Saftey set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of investigational product. This analysis set was used for the safety analyses	
Subject analysis set title	PK set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PK Set (only for the PK sub-study): all randomised subjects who had evaluable PK data readouts. This analysis set was used for the PK analysis;	

Primary: Schirmer’s test type II (with anaesthesia) result

End point title	Schirmer’s test type II (with anaesthesia) result
End point description:	
Schirmer's test was performed to measure basal aqueous tear secretion following the instillation of a preservative-free anaesthetic eye drop. Both eyes could be tested at the same time. Schirmer’s plus® strips were used. This test was conducted in a dimly lit room. While the patient looked upwards, the lower lid was drawn downwards gently and temporally. The rounded bent end of a sterile strip was inserted in the lower conjunctival sac over the temporal one-third of the lower eyelid margin. The test was to be done without touching directly the Schirmer’s test strip with the fingers to avoid contamination of skin oils. The patients were instructed to close their eyes gently. After a 5-min elapse, the Schirmer’s test strip was removed and the length of the tear absorption on the strip measured (as mm/5 min). The wetting distance at 5 min for each eye was recorded in the CRF.	
End point type	Primary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: mm/5 min				
arithmetic mean (standard deviation)	9.6 (± 7.2)	6.8 (± 5.7)	9.6 (± 4.4)	8.6 (± 5.3)

Statistical analyses

Statistical analysis title	Wilcoxon rank

Statistical analysis description:

Statistical analysis on changes from baseline between groups and in changes from baseline within groups

Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Wilcoxon Rank Sum Test

Notes:

[1] - No significant changes among groups. Significant changes at all post-dose times as compared to baseline values

Statistical analysis title	Chi-square

Statistical analysis description:

Pairwise comparisons were performed only if the null global hypothesis of equal success proportions in the four treatment groups was rejected and in this case $\chi 2$ tests for contingency tables with an alpha level of 0.05 was performed for the following comparisons and according to the following comparison order:

1 Group 3 (RP101 0.1% + RP101 0.1%) vs. Group 4 (Placebo + Placebo);
2 Group 2 (RP101 0.1% + Placebo) vs. Group 4 (Placebo + Placebo);
3 Group 1 (RP101 0.05% + RP101 0.05%) vs. Group

Comparison groups	Treatment group 2 v Treatment group 3 v Treatment group 1 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	≤ 0.05
Method	Chi-squared

Notes:

[2] - No significant difference in success proportions between groups

Secondary: Ocular tolerability foreign body sensation

End point title	Ocular tolerability foreign body sensation

End point description:

Assessed by the patients using a 0-100 mm visual analogue scale

End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: mm				
arithmetic mean (standard deviation)	15.5 (± 14.9)	12.9 (± 19.2)	19.1 (± 16.6)	23.3 (± 23.0)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - burning/stinging

End point title	Ocular tolerability - burning/stinging
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: mm				
arithmetic mean (standard deviation)	17.9 (± 15.8)	8.8 (± 14.7)	19.6 (± 17.0)	27.2 (± 26.9)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - itching

End point title	Ocular tolerability - itching
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: mm				
arithmetic mean (standard deviation)	15.6 (± 12.8)	9.2 (± 9.4)	14.5 (± 13.9)	18.6 (± 18.0)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - Pain

End point title	Ocular tolerability - Pain
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: second				
arithmetic mean (standard deviation)	9.9 (± 10.5)	4.8 (± 5.0)	14.3 (± 15.1)	13.8 (± 14.8)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - sticky feeling

End point title	Ocular tolerability - sticky feeling
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: millimetre(s)				
arithmetic mean (standard deviation)	19.5 (± 22)	6.5 (± 6.1)	16.1 (± 20.4)	24.0 (± 21.4)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - blurred vision

End point title	Ocular tolerability - blurred vision
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: millimetre(s)				
arithmetic mean (standard deviation)	25.5 (± 23.4)	22.1 (± 22.3)	29.0 (± 20.3)	26.2 (± 22.9)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - redness

End point title	Ocular tolerability - redness

End point description:

Assessed by the patients using a 0-100 mm visual analogue scale

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: millimetre(s)				
arithmetic mean (standard deviation)	20.7 (± 20.7)	9.6 (± 10.1)	13.8 (± 12.9)	16.0 (± 13.7)

Statistical analyses

Statistical analysis title	Wilcoxon rank

Statistical analysis description:

Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group

Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - tearing

End point title	Ocular tolerability - tearing

End point description:

Assessed by the patients using a 0-100 mm visual analogue scale

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: millimetre(s)				
arithmetic mean (standard deviation)	17.4 (± 13.7)	12.3 (± 11.7)	17.6 (± 16.9)	21.9 (± 23.8)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description: Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Ocular tolerability - eyelid swelling

End point title	Ocular tolerability - eyelid swelling
End point description: Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe: 3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: millimetre(s)				
arithmetic mean (standard deviation)	11.8 (± 11.6)	7.1 (± 8.8)	11.4 (± 9.1)	15.6 (± 18.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular tolerability - photophobia	
End point title	Ocular tolerability - photophobia
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	8	18
Units: millimetre(s)				
arithmetic mean (standard deviation)	16.7 (± 12.7)	15.5 (± 19.9)	19.1 (± 15.9)	29.8 (± 31.3)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description:	
Comparison of changes from baseline between groups and comparison at each assessment time-point versus baseline within group	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Symptom Assessment in Dry Eye - frequency	
End point title	Symptom Assessment in Dry Eye - frequency
End point description:	
Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: millimetre(s)				
arithmetic mean (standard deviation)	20.4 (± 13.0)	19.8 (± 18.1)	26.3 (± 23.1)	28.6 (± 15.4)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description: 11.1.3 Symptom Assessment in Dry Eye	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Symptom Assessment in Dry Eye - severity

End point title	Symptom Assessment in Dry Eye - severity
End point description: Assessed by the patients using a 0-100 mm visual analogue scale	
End point type	Secondary
End point timeframe: 3 months	

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: millimetre(s)				
arithmetic mean (standard deviation)	22.9 (± 15.3)	20.0 (± 19.0)	23.8 (± 17.5)	29.2 (± 14.4)

Statistical analyses

Statistical analysis title	Wilcoxon rank
Statistical analysis description: Comparison of changes from baseline between groups and comparison at each post-dose assessment time versus baseline	
Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Tear film break up time (TFBUT)

End point title	Tear film break up time (TFBUT)

End point description:

TFBUT was measured after instillation of sodium fluorescein solution in the inferior conjunctival cul-de-sac of each eye. The patient was instructed to blink several times to thoroughly mix the fluorescein with the tear film. In order to achieve maximum fluorescence, the examiner waited approximately 30 sec after instillation before evaluating TFBUT. With the aid of a slit lamp, the examiner monitored the integrity of the tear film, noting the time to form lacunae (clear spaces in the tear film) from the time that the eye was open after the last blink. The TFBUT was measured twice during the first minute after fluorescein instillation. If the 2 readings differed by more than 2 sec a third reading was to be taken. The TFBUT value was the average of the 2 or 3 measurements

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: second				
arithmetic mean (standard deviation)	4.6 (± 1.0)	4.7 (± 3.0)	4.1 (± 0.9)	5.9 (± 5.7)

Statistical analyses

Statistical analysis title	Wilcoxon rank

Statistical analysis description:

Comparison of changes from baseline between groups and comparison at each post-dose assessment time versus baseline

Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Visual acuity

End point title	Visual acuity

End point description:

Visual acuity was measured using retroilluminated light box and ETDRS 4 meter distance acuity charts. If 20 or more letters were read at 4 metres, the visual acuity score was recorded as the number of letters correct at 4 metres plus 30. If no letters were correctly read at either 4 metres or 1 metre, then the visual acuity score was to be recorded as "0".

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: millimetre(s)				
arithmetic mean (standard deviation)	82.4 (± 7.2)	74.9 (± 18.3)	82.0 (± 4.4)	81.8 (± 6.7)

Statistical analyses

Statistical analysis title	Wilcoxon rank

Statistical analysis description:

Comparison of changes from baseline between groups and comparison at each post-dose assessment time versus baseline

Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: SLE - Eyelid - Meibomian Glands

End point title	SLE - Eyelid - Meibomian Glands

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-3 score scale:
Eyelid - Meibomian glands (evaluation of the central 10 Meibomian gland openings in the mid-portion of the upper eyelid) with 0 = None (none are plugged); 1 = Mild (1 to 2 glands are plugged); 2 = Moderate (3 to 4 glands are plugged); 3 = Severe (All glands are plugged).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0.1 (± 0.3)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - Eyelid - erythema

End point title	SLE - Eyelid - erythema

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-4 score scale:

Eyelid - Erythema, with 0 = None (normal); 1 = Mild (redness localised to a small region of the lid(s) margin OR skin); 2 = Moderate (redness of most or all lid margin OR skin); 3 = Severe (redness of most or all lid margin AND skin); 4 = Very severe (marked diffuse redness of both lid margin AND skin).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0.2 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - Eyelid - Oedema

End point title	SLE - Eyelid - Oedema

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-4 score scale:
Eyelid - Oedema with 0 = None (normal); 1 = Mild (localised to a small region of the lid); 2 = Moderate (diffuse, most or all lid but not prominent/protruding); 3 = Severe (diffuse, most or all lid AND prominent/protruding); 4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.1 (± 0.2)	0 (± 0)	0 (± 0)	0.1 (± 0.3)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - conjunctiva - erythema

End point title	SLE - conjunctiva - erythema

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-3 score scale:

Conjunctiva - Erythema with 0 = None (normal); 1 = Mild (a flush reddish colour predominantly confined to the palpebral or bulbar conjunctiva); 2 = Moderate (more prominent red colour of the palpebral or bulbar conjunctiva); 3 = Severe (definite redness of palpebral or bulbar conjunctiva).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.4 (± 0.6)	0.4 (± 0.5)	0.5 (± 0.7)	0.5 (± 0.7)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - Conjunctiva - oedema

End point title	SLE - Conjunctiva - oedema

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-4 score scale:

Conjunctiva - Oedema with 0 = None (normal); 1 = Mild (slight localised swelling); 2 = Moderate (moderate/medium localised swelling or mild diffuse swelling); 3 = Severe (severe diffuse swelling); 4 = Very severe (very prominent/protruding diffuse swelling).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.1 (± 0.3)	0.2 (± 0.4)	0.1 (± 0.3)	0.2 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - Lens

End point title	SLE - Lens

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-3 score scale:

Lens with 0 = No opacification (normal lens); 1 = Mild lens opacification; 2 = Moderate lens opacification; 3 = Severe lens opacification; N/A = Patient with artificial lens

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.1 (± 0.3)	0.3 (± 0.7)	0 (± 0)	0.2 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Secondary: SLE - Anterior Chamber Inflammation

End point title	SLE - Anterior Chamber Inflammation

End point description:

The SLE was performed before the instillation of any dilating or anaesthetic eye drops or fluorescein agent. For the examination, the patient sat at the slit lamp. Grading of the eyelids, conjunctiva, cornea, lens and anterior chamber was done according to the following 0-3 score scale:

Anterior Chamber Inflammation (Slit beam = 0.3 mm wide, 1.0 mm long) with 0 = None (no Tyndall effect); 1 = Mild (Tyndall effect barely discernible); 2 = Moderate (Tyndall beam in the anterior chamber is moderately intense); 3 = Severe (Tyndall beam in the anterior chamber is severely intense).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Corneal fluorescein staining

End point title	Corneal fluorescein staining

End point description:

Corneal fluorescein staining was graded using the Oxford scheme to evaluate cornea and conjunctiva epithelium damage. The examination was performed after instillation of sodium fluorescein in the inferior conjunctival cul-de-sac of each eye with the aid of a slit lamp.
As grading scale of the corneal damage, the NEI/Industry Workshop guideline was used. The cornea was divided into five sectors (central, superior, inferior, nasal and temporal), each of which was scored on a scale of 0–3, with a maximal global score of 15 (total score, here reported).

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: Total score				
arithmetic mean (standard deviation)	2.9 (± 1.7)	3.3 (± 2.0)	3.4 (± 1.9)	2.8 (± 1.9)

Statistical analyses

Statistical analysis title	Wilcoxon rank

Statistical analysis description:

Comparison of changes from baseline between groups and comparison at each post-dose assessment time versus baseline within groups

Comparison groups	Treatment group 1 v Treatment group 2 v Treatment group 3 v Treatment group 4
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon Rank Test

Secondary: Fundus ophthalmoscopy - Vitreous

End point title	Fundus ophthalmoscopy - Vitreous

End point description:

The fundus examination included ophthalmoscopic assessments of vitreous, macula, retina and optic nerve head. Vitreous examination results were scored according to the following grading criteria:

Vitreous: The examiner judged the appearance of the vitreous in the visual axis as Normal (score 0): Absence of any opacity or Abnormal (score 1): Presence of opacity in the vitreous.

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0.2)	0 (± 0)	0 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Fundus ophthalmoscopy - Macula, retina, optic nerve head

End point title	Fundus ophthalmoscopy - Macula, retina, optic nerve head

End point description:

The fundus examination included ophthalmoscopic assessments of vitreous, macula, retina and optic nerve head. Macula, retina and optic nerve head examination results were scored according to the following grading criteria:
Macula, (Peripheral) Retina and Optic Nerve Head: The examiner provided a separate assessment of the macular, choroid and peripheral retina as Normal (score 0): Absence of any structural or vascular change, inflammation, oedema or haemorrhage or Abnormal (score 1): Evidence of any ongoing or previous structural or vascular change, inflammation, oedema or haemorrhage.

End point type	Secondary

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: scores				
arithmetic mean (standard deviation)	0.3 (± 0.5)	0.5 (± 0.5)	0.5 (± 0.5)	0.5 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Corneal pachimetry

End point title	Corneal pachimetry

End point description:

Sub-study on 36 of the enrolled patients

End point type	Other pre-specified

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	2	8
Units: micrometre(s)				
arithmetic mean (standard deviation)	563 (± 35.6)	574.8 (± 17.4)	597 (± 22.6)	560.1 (± 25.5)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Serum estradiol concentrations

End point title	Serum estradiol concentrations

End point description:

Blood samples for estardiol concentrations measurements were collected at baseline and at day 90 (study end). Serum samples were prepared and the concentration of estradiol in serum was determined at a specified analytical laboratory, using a fully validated LC-MS/MS method, with a lower quantification limit (LQL) of 5.00 pg/mL.

End point type	Other pre-specified

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	8	12
Units: picograms/milliliters				
arithmetic mean (standard deviation)	14.53 (± 14.77)	27.12 (± 22.40)	33.92 (± 15.95)	0 (± 5.7)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Intraocular pressure

End point title	Intraocular pressure

End point description:

Safety endpoint

IOP was measured as a safety variable using an applanation tonometry after the instillation of a topical anaesthetic. IOP was measured after completion of all other examinations to avoid potential interference . The patient’s head was firmly positioned on the chin rest and against the forehead rest without leaning forward or straining.

End point type	Other pre-specified

End point timeframe:

3 months

End point values	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	13	22
Units: mmHg				
arithmetic mean (standard deviation)	15.75 (± 1.65)	14.82 (± 1.71)	15.77 (± 1.36)	15.05 (± 1.70)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the signature of the informed consent until the last follow-up	
Adverse event reporting additional description:	
Adverse events (AEs) were coded by System Organ Class (SOC) and Preferred Term (PT), using the MedDRA 22.1. AEs were classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Group 1: RP101 0.05% + RP101 0.05%	
Reporting group title	Group 2
Reporting group description:	
Group 2: RP101 0.1% + Placebo	
Reporting group title	Group 3
Reporting group description:	
Group 3: RP101 0.1% + RP101 0.1%	
Reporting group title	Group 4
Reporting group description:	
Group 4: Placebo + Placebo	

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Group 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 27 (70.37%)	18 / 25 (72.00%)	18 / 26 (69.23%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	3 / 26 (11.54%)
occurrences (all)	1	5	5
Eye disorders			
Vision blurred			
subjects affected / exposed	14 / 27 (51.85%)	13 / 25 (52.00%)	11 / 26 (42.31%)
occurrences (all)	23	26	18
Eye pain			
subjects affected / exposed	10 / 27 (37.04%)	9 / 25 (36.00%)	6 / 26 (23.08%)
occurrences (all)	14	17	8
Eye irritation			
subjects affected / exposed	4 / 27 (14.81%)	4 / 25 (16.00%)	4 / 26 (15.38%)
occurrences (all)	5	8	4
Ocular hyperaemia			
subjects affected / exposed	7 / 27 (25.93%)	4 / 25 (16.00%)	3 / 26 (11.54%)
occurrences (all)	8	7	4
Swelling of eyelid			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	2 / 26 (7.69%)
occurrences (all)	4	2	2
Foreign body sensation in eyes			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	3 / 26 (11.54%)
occurrences (all)	1	4	4
Photophobia			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	1 / 26 (3.85%)
occurrences (all)	2	5	1
Eye pruritus			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Lacrimation increased			

subjects affected / exposed	0 / 27 (0.00%)	3 / 25 (12.00%)	2 / 26 (7.69%)
occurrences (all)	0	3	3
Abnormal sensation in eye			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Eye oedema			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Eye swelling			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	2 / 26 (7.69%)
occurrences (all)	0	1	3
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	3

Non-serious adverse events	Group 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 26 (61.54%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			
subjects affected / exposed	9 / 26 (34.62%)		
occurrences (all)	12		
Eye pain			

subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	6		
Eye irritation			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	5		
Ocular hyperaemia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	6		
Swelling of eyelid			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Foreign body sensation in eyes			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Eye pruritus			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Lacrimation increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	3		
Abnormal sensation in eye			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Eye oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Eye swelling			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported