Clinical trial results:
A MULTICENTER, RANDOMIZED, DOUBLE-MASKED, 3 PARALLEL ARMS,PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF NOVA22007 1MG/ML (CICLOSPORIN/CYCLOSPORINE) EYE DROPS,EMULSION ADMINISTERED IN PAEDIATRIC PATIENTS WITH ACTIVE SEVERE VERNAL KERATOCONJUNCTIVITIS WITH SEVERE KERATITIS

Summary

EudraCT number	2012-005060-10
Trial protocol	HU IT DE PT ES GR HR FR
Global end of trial date	01 February 2016

Results information

Result version number	v1 (current)
This version publication date	07 April 2023
First version publication date	07 April 2023

Trial information

Trial identification

Sponsor protocol code	NVG09B113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01751126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santen Sas
Sponsor organisation address	Genavenir IV, 1 rue Pierre Fontaine , Evry, France,
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Scientific contact	Mourad Amrane, Santen SAS, 331 69874022, mourad.amrane@santen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000575-PIP01-09
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	01 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2016
Global end of trial reached?	Yes
Global end of trial date	01 February 2016
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 compare the efficacy of two different dosing regimens of NOVA22007 (1mg/ml ciclosporin/cyclosporine) eye drops, emulsion versus placebo (vehicle of the formulation) administered four times a day in patients with severe VKC after 4 months of treatment.

Protection of trial subjects:

Dexamethasone 0.1% eye drops provided by the sponsor will be dispensed by the investigator to the patient during the course of the study treatment only in case of keratitis worsening of at least one grade on the modified Oxford scale or maintained during 2 months at the entry level and/or symptom worsening of at least 1 centimeter on at least one of the four symptoms along with the worsening of the mean of the 4 symptoms or maintenance at the entry level of the mean VAS of the 4 symptoms. The dosing instructions will be 1 drop 4 times daily for 5 days and a maximum of 2 courses between two scheduled visits during the treatment period and a maximum of 4 courses between two scheduled visits during the 8 month safety period. The rescue therapy will have to be given at least 30 minutes before or after the study medication. To reduce the systemic absorption a nasolacrimal occlusion by compression of lacrimal ducts should be applied after the instillation.
The rescue therapy need and prescription will have to be documented by the investigator during a visit. If the patient is unable to reach the investigator for a visit the patient will be allowed to use unpreserved artificial tears taken up to 4 times a day until a visit is scheduled.

Background therapy:

None

Evidence for comparator:

A placebo arm was deemed appropriate as there is no acknowledged standard treatment for VKC. Also the design of the study allows a reduced number of children that have to be recruited for a well-recognized rare disease.
The placebo arm will not be a strict untreated arm as the vehicle will be administered and also the investigator will have the possibility to give a rescue medication: dexamethasone 0.1% 4 times a day for 5 days provided that the patient satisfies the condition for rescue medication prescription: in case of keratitis worsening of at least one grade on the Modified Oxford Scale or maintained during 2 months at the entry level and/or symptom worsening of at least 1 centimeter on at least one of the four symptoms along with the worsening of the mean of the 4 symptoms or maintenance at the entry level of the mean VAS of the 4 symptoms.

Actual start date of recruitment	29 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	India: 34
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	168
EEA total number of subjects	100

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)	127
Adolescents (12-17 years)	41
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 169 patients were randomized into the study. These patients were recruited in 11 countries and a total of 101 patients were from Europe. One participant from the High dose regimen withdrew at the first week of randomization and not related to study medication. Therefore, the Full Analysis Set (FAS) consisted of 168 patients.

Period 1

Period 1 title	Period I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	NOVA22007 Ciclosporing 4 times at day

Arm description:

One drop of ciclosporin (NOVA22007) 1 mg/ml 4 times a day as monotherapy (morning, noon, afternoon and evening).

Arm type	Experimental
Investigational medicinal product name	NOVA22007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, emulsion
Routes of administration	Ocular use

Dosage and administration details:

For the group receiving the study medication 4 times a day 1 drop of the study medication NOVA22007 1 mg/mL CsA eye drops, emulsion in each eye 4 times daily: in the morning, at noon, in the afternoon and the evening.

Arm title	NOVA22007 Ciclosporin/Placebo twice daily

Arm description:

One drop of ciclosporin (NOVA22007) 1mg/ml twice a day and one drop of placebo twice a day (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.

Arm type	Experimental
Investigational medicinal product name	NOVA22007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ocular use

Dosage and administration details:

- For the group receiving the study medication twice a day

1 drop of the study medication NOVA22007 1mg/ml CsA eye drops, emulsion in each eye in the morning and evening and 1 drop of the placebo (vehicle of the study medication) at noon and in the afternoon.

Arm title	Placebo

Arm description:

One drop of placebo 4 times a day as monotherapy (morning, noon, afternoon and evening).

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

Dosage and administration details:

The placebo was the NOVA22007 vehicle which is a sterile, drug-free, cationic ophthalmic oil-in-water emulsion containing 0 mg/mL CsA. The formulation of placebo was exactly the same formulation as the NOVA22007 but excluded the active substance.
For the group receiving the placebo 4 times a day
1 drop of the placebo in each eye 4 times daily: in the morning, at noon, in the afternoon and evening.

Number of subjects in period 1	NOVA22007 Ciclosporing 4 times at day	NOVA22007 Ciclosporin/Placebo twice daily	Placebo
Started	56	54	58
Completed	50	43	49
Not completed	6	11	9
Patient decision unrelated to AE	2	3	2
Adverse event, non-fatal	2	-	2
Other	-	1	-
Investigator decision	1	1	-
Lost to follow-up	-	1	-
Lack of efficacy	1	5	5

Period 2

Period 2 title	Period II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	NOVA22007 Ciclosporing 4 times at day

Arm description:

One drop of ciclosporin (NOVA22007) 1 mg/ml 4 times a day as monotherapy (morning, noon, afternoon and evening).

Arm type	Experimental

Investigational medicinal product name	NOVA22007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ocular use

Dosage and administration details:

For the group receiving the study medication 4 times a day 1 drop of the study medication NOVA22007 1 mg/mL CsA eye drops, emulsion in each eye 4 times daily: in the morning, at noon, in the afternoon and the evening.

Arm title	NOVA22007 Ciclosporin/Placebo twice daily

Arm description:

One drop of ciclosporin (NOVA22007) 1mg/ml twice a day and one drop of placebo twice a day (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.

Arm type	Experimental
Investigational medicinal product name	NOVA22007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ocular use

Dosage and administration details:

For the group receiving the study medication twice a day
1 drop of the study medication NOVA22007 1mg/ml CsA eye drops, emulsion in each eye in the morning and evening and 1 drop of the placebo (vehicle of the study medication) at noon and in the afternoon.

Number of subjects in period 2	NOVA22007 Ciclosporing 4 times at day	NOVA22007 Ciclosporin/Placebo twice daily
Started	72	70
Completed	72	70

Baseline characteristics

Reporting groups	
Reporting group title	NOVA22007 Ciclosporing 4 times at day
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1 mg/ml 4 times a day as monotherapy (morning, noon, afternoon and evening).	
Reporting group title	NOVA22007 Ciclosporin/Placebo twice daily
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1mg/ml twice a day and one drop of placebo twice a day (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.	
Reporting group title	Placebo
Reporting group description:	
One drop of placebo 4 times a day as monotherapy (morning, noon, afternoon and evening).	

Reporting group values	NOVA22007 Ciclosporing 4 times at day	NOVA22007 Ciclosporin/Placebo twice daily	Placebo
Number of subjects	56	54	58
Age categorical 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			
Children (4-18 years)			
Units: years arithmetic mean standard deviation	 9.1 ± 3.3	 9.6 ± 3.4	 8.9 ± 3.2
Gender categorical Units: Subjects			
Female Male	12 44	12 42	12 46

Reporting group values	Total		
Number of subjects	168		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)	0 0 0 0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Children (4-18 years)			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	36		
Male	132		

End points

End points reporting groups

Reporting group title	NOVA22007 Ciclosporing 4 times at day
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1 mg/ml 4 times a day as monotherapy (morning, noon, afternoon and evening).	
Reporting group title	NOVA22007 Ciclosporin/Placebo twice daily
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1mg/ml twice a day and one drop of placebo twice a day (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.	
Reporting group title	Placebo
Reporting group description:	
One drop of placebo 4 times a day as monotherapy (morning, noon, afternoon and evening).	
Reporting group title	NOVA22007 Ciclosporing 4 times at day
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1 mg/ml 4 times a day as monotherapy (morning, noon, afternoon and evening).	

Reporting group title	NOVA22007 Ciclosporin/Placebo twice daily
Reporting group description:	
One drop of ciclosporin (NOVA22007) 1mg/ml twice a day and one drop of placebo twice a day (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.	
Subject analysis set title	LogMAR - High Dose Regimen
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	
Subject analysis set title	LogMAR - Low Dose Regimen
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	
Subject analysis set title	LogMAR-Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	
Subject analysis set title	Change From Baseline in LogMARHigh Dose
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	
Subject analysis set title	Change From Baseline in LogMARLow Dose
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	
Subject analysis set title	Change From Baseline in LogMARPlacebo
Subject analysis set type	Full analysis
Subject analysis set description:	
This group has the randomized population (SS).	

Primary: Composite efficacy score

End point title	Composite efficacy score

End point description:

End point type	Primary

End point timeframe:

over the 4months

End point values	NOVA22007 Ciclosporing 4 times at day	NOVA22007 Ciclosporin/Placebo twice daily	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	54	58	
Units: penalties adjusted CFS				
arithmetic mean (standard deviation)	2.06 (± 1.44)	1.93 (± 1.37)	1.34 (± 1.22)	

Statistical analyses

Statistical analysis title	Superiority test1

Statistical analysis description:

Claim superiority of the active treatment over placebo in the primary endpoint.

Comparison groups	NOVA22007 Ciclosporing 4 times at day v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [1]
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.27

Notes:

[1] - ANCOVA with treatment as well the baseline CFS and the exposure to VKC seasons (Hochberg procedure)

Statistical analysis title	Superiority test2

Statistical analysis description:

Claim superiority of the active treatment- low dose over placebo in the primary endpoint.

Comparison groups	Placebo v NOVA22007 Ciclosporin/Placebo twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [2]
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.18

Notes:

[2] - ANCOVA with treatment as well the baseline CFS and the exposure to VKC seasons (Hochberg procedure)

Secondary: Number of Courses of Rescue Medication in Period I

End point title	Number of Courses of Rescue Medication in Period I

End point description:

End point type	Secondary

End point timeframe:

Up to 4-Month

End point values	NOVA22007 Ciclosporing 4 times at day	NOVA22007 Ciclosporin/Placebo twice daily	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	54	58	
Units: Number of courses				
Month1, zero course	51	41	44	
Month 1, one course	3	7	11	
Month1, two courses	0	2	2	
Month2, zero course	45	43	38	
Month 2, one course	6	2	11	
Month 2, two courses	2	2	3	
Month3, zero course	43	42	34	
Month3, one course	7	2	12	
Month 3, two courses	1	2	4	
Month4, zero course	42	41	38	
Month4, one course	6	2	8	
Month 4, two courses	2	1	2	
Month 4/Early Termination, zero course	46	46	43	
Month 4/Early Termination, one course	7	5	11	
Month 4/Early Termination, two course	3	3	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Corrected Distance Visual Acuity (BCDVA) in 4-month Randomized Period I

End point title	Best Corrected Distance Visual Acuity (BCDVA) in 4-month Randomized Period I

End point description:

End point type	Secondary

End point timeframe:

Up to Month 4/Early Termination

End point values	LogMAR - High Dose Regimen	LogMAR - Low Dose Regimen	LogMAR-Placebo	Change From Baseline in LogMARHigh Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	54	58	57
Units: Letters				
arithmetic mean (standard deviation)				
Baseline	0.293 (± 0.297)	0.209 (± 0.284)	0.302 (± 0.347)	0 (± 0)
Month 1	0.263 (± 0.292)	0.160 (± 0.241)	0.285 (± 0.362)	-0.036 (± 0.187)
Month 2	0.221 (± 0.251)	0.146 (± 0.214)	0.331 (± 0.352)	-0.071 (± 0.191)
Month 3	0.172 (± 0.235)	0.110 (± 0.204)	0.273 (± 0.318)	-0.110 (± 0.173)
Month 4	0.149 (± 0.244)	0.097 (± 0.203)	0.237 (± 0.308)	-0.127 (± 0.165)
Month 4/Early Termination	0.158 (± 0.249)	0.114 (± 0.212)	0.217 (± 0.295)	-0.135 (± 0.220)

End point values	Change From Baseline in LogMARLow Dose	Change From Baseline in LogMARPlacebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	58		
Units: Letters				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	0 (± 0)		
Month 1	-0.058 (± 0.199)	-0.027 (± 0.182)		
Month 2	-0.073 (± 0.202)	0.003 (± 0.233)		
Month 3	-0.089 (± 0.233)	-0.066 (± 0.229)		
Month 4	-0.110 (± 0.233)	-0.109 (± 0.211)		

Month 4/Early Termination	-0.091 (± 0.257)	-0.097 (± 0.210)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Corrected Distance Visual Acuity (BCDVA) in 4-month Randomized Period II

End point title	Best Corrected Distance Visual Acuity (BCDVA) in 4-month Randomized Period II

End point description:

End point type	Secondary

End point timeframe:

Up to Month 12/Early Termination

End point values	LogMAR - High Dose Regimen	LogMAR - Low Dose Regimen	LogMAR-Placebo	Change From Baseline in LogMARHigh Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	22	72	50
Units: Letters				
arithmetic mean (standard deviation)				
Baseline (Month 4)	0.152 (± 0.246)	0.250 (± 0.317)	0.181 (± 0.270)	0 (± 0)
Month 6	0.128 (± 0.230)	0.258 (± 0.359)	0.168 (± 0.280)	-0.024 (± 0.114)
Month 8	0.141 (± 0.228)	0.222 (± 0.324)	0.165 (± 0.261)	-0.015 (± 0.136)
Month 10	0.141 (± 0.222)	0.207 (± 0.325)	0.160 (± 0.257)	-0.014 (± 0.149)
Month 12	0.134 (± 0.214)	0.220 (± 0.363)	0.160 (± 0.268)	-0.020 (± 0.152)
Month 12/Early Termination	0.136 (± 0.212)	0.220 (± 0.363)	0.161 (± 0.266)	-0.016 (± 0.154)

End point values	Change From Baseline in LogMARLow Dose	Change From Baseline in LogMARPlacebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	72		
Units: Letters				
arithmetic mean (standard deviation)				
Baseline (Month 4)	0 (± 0)	0 (± 0)		

Month 6	-0.017 (± 0.143)	-0.022 (± 0.122)		
Month 8	-0.029 (± 0.155)	-0.019 (± 0.141)		
Month 10	-0.044 (± 0.128)	-0.023 (± 0.143)		
Month 12	-0.030 (± 0.172)	-0.023 (± 0.157)		
Month 12/Early Termination	-0.030 (± 0.172)	-0.020 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the informed consent form was signed until the last study visit at Month 12.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	1) High Dose in period I plus High Dose in period II

Reporting group description:

.1% QID (4 Months) Plus .1% QID (8 Months Safety Follow-up)
Participants in this group received High dose in Period I (4 months) and continuing in High dose in the follow up period (8 months).

Reporting group title	2) Vehicle in period I plus High Dose in period II

Reporting group description:

Vehicle QID (4 Months) Plus .1% QID (8 Months Safety Follow-up)
Participants in this group received Placebo in Period I (4 months) and continuing in High dose in the follow up period (8 months).

Reporting group title	3) Total High Dose

Reporting group description:

Total of participants that received High dose from the overall study period (0-12 months).

Reporting group title	4) Low Dose in period I plus Low Dose in period II

Reporting group description:

.1% BID + Vehicle BID (4 Months) Plus .1% BID+ Vehicle BID (8 Months Safety Follow-up)
Participants in this group received Low dose in Period I (4 months) and continuing in Low dose in the follow up period (8 months).

Reporting group title	5) Vehicle in period I plus Low Dose in period II

Reporting group description:

Vehicle QID (4 Months) Plus .1% BID+ Vehicle BID (8 Months Safety Follow-up)
Participants in this group received Placebo in Period I (4 months) and continuing in Low dose in the follow up period (8 months).

Reporting group title	6) Total Low Dose

Reporting group description:

Total of participants that received Low dose from the overall study period (0-12 months).

Serious adverse events	1) High Dose in period I plus High Dose in period II	2) Vehicle in period I plus High Dose in period II	3) Total High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)	0 / 22 (0.00%)	3 / 72 (4.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			

subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	4) Low Dose in period I plus Low Dose in period II	5) Vehicle in period I plus Low Dose in period II	6) Total Low Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Phimosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	1) High Dose in period I plus High Dose in period II	2) Vehicle in period I plus High Dose in period II	3) Total High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 50 (58.00%)	13 / 22 (59.09%)	42 / 72 (58.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Surgical and medical procedures			
Removal of internal fixation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Application site discharge			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	2	2
Application site erosion			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Application site swelling			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Instillation site erythema			

subjects affected / exposed	1 / 50 (2.00%)	2 / 22 (9.09%)	3 / 72 (4.17%)
occurrences (all)	1	5	6
Instillation site foreign body sensation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Instillation site lacrimation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Instillation site pain			
subjects affected / exposed	6 / 50 (12.00%)	4 / 22 (18.18%)	10 / 72 (13.89%)
occurrences (all)	7	5	12
Instillation site pruritus			
subjects affected / exposed	2 / 50 (4.00%)	3 / 22 (13.64%)	5 / 72 (6.94%)
occurrences (all)	2	6	8
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Asthma			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	3 / 50 (6.00%)	1 / 22 (4.55%)	4 / 72 (5.56%)
occurrences (all)	3	1	4

Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	2	0	2
Rhinitis allergic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Sneezing			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Intraocular pressure decreased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Intraocular pressure increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Protein total increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 50 (8.00%)	1 / 22 (4.55%)	5 / 72 (6.94%)
occurrences (all)	6	1	7

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Blepharitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Cataract subcapsular			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Conjunctival irritation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Conjunctivitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Corneal deposits			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Corneal leukoma			
subjects affected / exposed	2 / 50 (4.00%)	0 / 22 (0.00%)	2 / 72 (2.78%)
occurrences (all)	3	0	3
Corneal neovascularisation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Erythema of eyelid			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Eye irritation			

subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Eye pruritus			
subjects affected / exposed	0 / 50 (0.00%)	3 / 22 (13.64%)	3 / 72 (4.17%)
occurrences (all)	0	3	3
Eyelid erosion			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Eyelid oedema			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Eyelid ptosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Foreign body sensation in eyes			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Lacrimation increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Meibomianitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Ocular discomfort			
subjects affected / exposed	0 / 50 (0.00%)	2 / 22 (9.09%)	2 / 72 (2.78%)
occurrences (all)	0	2	2
Ocular hyperaemia			
subjects affected / exposed	2 / 50 (4.00%)	2 / 22 (9.09%)	4 / 72 (5.56%)
occurrences (all)	4	2	6
Pharyngitis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 22 (0.00%)	2 / 72 (2.78%)
occurrences (all)	2	0	2
Ulcerative keratitis			

subjects affected / exposed	2 / 50 (4.00%)	0 / 22 (0.00%)	2 / 72 (2.78%)
occurrences (all)	3	0	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Aphthous stomatitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	3	3
Dermatitis atopic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Eczema			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Papule			

subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Rash generalised			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Growing pains			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	4	4
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	1
Conjunctivitis viral			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Eye infection bacterial			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Hordeolum			

subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	4 / 50 (8.00%)	0 / 22 (0.00%)	4 / 72 (5.56%)
occurrences (all)	4	0	4
Laryngitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 22 (0.00%)	3 / 72 (4.17%)
occurrences (all)	6	0	6
Otitis externa			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Parasitic gastroenteritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 22 (0.00%)	2 / 72 (2.78%)
occurrences (all)	2	0	2
Tooth abscess			
subjects affected / exposed	1 / 50 (2.00%)	0 / 22 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Upper respiratory tract infection			

subjects affected / exposed	2 / 50 (4.00%)	0 / 22 (0.00%)	2 / 72 (2.78%)
occurrences (all)	2	0	2
Varicella			
subjects affected / exposed	0 / 50 (0.00%)	1 / 22 (4.55%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 22 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	4) Low Dose in period I plus Low Dose in period II	5) Vehicle in period I plus Low Dose in period II	6) Total Low Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 44 (54.55%)	11 / 26 (42.31%)	35 / 70 (50.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Removal of internal fixation			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Application site discharge			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Application site erosion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Application site swelling			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Instillation site erythema			
subjects affected / exposed	2 / 44 (4.55%)	0 / 26 (0.00%)	2 / 70 (2.86%)
occurrences (all)	2	0	2
Instillation site foreign body sensation			

subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Instillation site lacrimation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Instillation site pain			
subjects affected / exposed	5 / 44 (11.36%)	0 / 26 (0.00%)	5 / 70 (7.14%)
occurrences (all)	10	0	10
Instillation site pruritus			
subjects affected / exposed	4 / 44 (9.09%)	0 / 26 (0.00%)	4 / 70 (5.71%)
occurrences (all)	4	0	4
Pyrexia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 26 (3.85%)	3 / 70 (4.29%)
occurrences (all)	2	1	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory disease			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	1 / 44 (2.27%)	1 / 26 (3.85%)	2 / 70 (2.86%)
occurrences (all)	2	1	3
Cough			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 26 (3.85%)	2 / 70 (2.86%)
occurrences (all)	1	1	2
Rhinitis allergic			

subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Intraocular pressure decreased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	2	0	2
Intraocular pressure increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Protein total increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0

Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Cataract subcapsular			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Conjunctival irritation			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Corneal deposits			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Corneal leukoma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	3	3
Corneal neovascularisation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Diplopia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Erythema of eyelid			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eye irritation			
subjects affected / exposed	1 / 44 (2.27%)	1 / 26 (3.85%)	2 / 70 (2.86%)
occurrences (all)	1	1	2
Eye pain			

subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Eyelid erosion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eyelid ptosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Foreign body sensation in eyes			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Lacrimation increased			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Meibomianitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Ocular discomfort			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 44 (0.00%)	2 / 26 (7.69%)	2 / 70 (2.86%)
occurrences (all)	0	5	5
Ulcerative keratitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Aphthous stomatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Oral pain			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Dermatitis allergic			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Papule			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	1 / 44 (2.27%)	1 / 26 (3.85%)	2 / 70 (2.86%)
occurrences (all)	1	1	2
Rash generalised			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Growing pains			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 26 (3.85%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis viral			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Eye infection bacterial			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Folliculitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Hordeolum			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Influenza			

subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	5 / 44 (11.36%)	1 / 26 (3.85%)	6 / 70 (8.57%)
occurrences (all)	6	2	8
Otitis externa			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Parasitic gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	2	2
Sinusitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 26 (3.85%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	2 / 44 (4.55%)	0 / 26 (0.00%)	2 / 70 (2.86%)
occurrences (all)	2	0	2
Tooth abscess			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Varicella			

subjects affected / exposed	0 / 44 (0.00%)	0 / 26 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 26 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2013	This amendment addressed the following changes based on the change requests after the single application: • Adding exclusion criterion 4: "History of ocular varicella-zoster or vaccinia virus infection." • Adding the procedure that patients receiving rescue medication are needed to have the IOP measured at each study visit. • Adding an explanation on the method to reduce systemic absorption of rescue therapy by nasolacrimal occlusion using compression of lacrimal ducts. • Adding of the QUICK questionnaire for the assessment of QoL.
02 January 2014	This amendment was country specific for Croatia .Modification of inclusion criterion 3 to match country specific requirements (related to contraception).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported