Clinical trial results:
A Phase IIIb, prospective, interventional, multicentre, three-year study to explore the long-term evolution of sign and symptoms, and occurrence of complications in Dry Eye Disease patients with severe keratitis receiving IKERVIS® (1mg/ml ciclosporin) eye drops

Summary

EudraCT number	2017-002660-41
Trial protocol	CZ PL IT
Global end of trial date	14 July 2023

Results information

Result version number	v1 (current)
This version publication date	17 March 2024
First version publication date	17 March 2024

Trial information

Trial identification

Sponsor protocol code	NVG14L127

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04144413
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santen S.A.S.
Sponsor organisation address	1 Rue Pierre Fontaine, Genavenir IV, 91058 Evry cedex, France, F-91058
Public contact	Global Regulatory Affairs Europe, SANTEN SAS, regulatoryaffairs@santen.com
Scientific contact	Global Regulatory Affairs Europe, SANTEN SAS, regulatoryaffairs@santen.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	05 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the long-term efficacy of a continuous treatment of IKERVIS® (1mg/mL ciclosporin) eye drops in adult dry eye disease (DED) patients with severe keratitis on corneal sign and DED symptoms, and to estimate the lag time (if any) to improvement in symptoms (if any)
2) To assess the ocular surface complications over the three-year study period.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its most recent update, and the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guideline. The study was also conducted in accordance with local legal and regulatory requirements of the countries involved, and with standard operating procedures in place.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 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	Poland: 83
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	Czechia: 65
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Russian Federation: 61
Country: Number of subjects enrolled	Türkiye: 10
Worldwide total number of subjects	350
EEA total number of subjects	279

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)	209
From 65 to 84 years	136
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 350 DED adult patients with severe keratitis having CFS grade 3 or above on the modified Oxford scale and with at least half of them having a CFS grade 4 or 5 were planned to be enrolled in approximately 52 trial sites in Period 1. It was expected that approximately 70% of the included patients would enter Period 2.

Period 1

Period 1 title	Open-Label Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	IKERVIS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion in single-dose container
Routes of administration	Ocular use

Dosage and administration details:

Instillation of one drop in each affected eye, once daily at bedtime. From Baseline for the first 12 months of treatment.

Number of subjects in period 1	Open-label
Started	350
Completed	288
Not completed	62
Adverse event, serious fatal	1
Consent withdrawn by subject	15
Non-compliance with Study Drug	2
Adverse event, non-fatal	26
Other	1
Lost to follow-up	2
Lack of efficacy	11
Protocol deviation	4

Period 2	
Period 2 title	Double-Masked Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Masked Ikervis
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	IKERVIS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion in single-dose container
Routes of administration	Ocular use
Dosage and administration details: Instillation of one drop in each affected eye, once daily at bedtime.	
Arm title	Masked Vehicle
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion in single-dose container
Routes of administration	Ocular use
Dosage and administration details: Instillation of one drop in each affected eye, once daily at bedtime.	

Number of subjects in period 2[1]	Masked Ikervis	Masked Vehicle
Started	148	97
Completed	137	86
Not completed	11	11
Adverse event, serious fatal	1	1
Non-compliance with Study Drug	3	1
Consent withdrawn by subject	6	3
Adverse event, non-fatal	1	1
Other	-	1
Lack of efficacy	-	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only Patients who have shown a marked improvement at Month 12 (as defined below) were randomised to receive IKERVIS® or Vehicle (ration 3:2) in double-masked fashion.

Baseline characteristics

Reporting groups

Reporting group title	Open-Label Treatment Period

Reporting group description: -

Reporting group values	Open-Label Treatment Period	Total	
Number of subjects	350	350	
Age categorical 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)	209	209	
From 65-84 years	136	136	
85 years and over	5	5	
Age continuous Units: years			
arithmetic mean	59.5		
standard deviation	± 13.24	-	
Gender categorical Units: Subjects			
Female	302	302	
Male	48	48	

End points

End points reporting groups	
Reporting group title	Open-label
Reporting group description: -	
Reporting group title	Masked Ikervis
Reporting group description: -	
Reporting group title	Masked Vehicle
Reporting group description: -	

Primary: The correlation CFS score and SANDE symptoms score in Period 1

End point title	The correlation CFS score and SANDE symptoms score in Period 1[1]

End point description:

The primary efficacy endpoint is the correlation between change from baseline in CFS score and SANDE symptoms score at each visit, and cross correlation of sign at visit X versus symptoms at visit X+i, if any.

End point type	Primary

End point timeframe:

Baseline visit (Day 1), Month 3, Month 6, Month 9, and Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical testing was conducted for this item measures in this study.

End point values	Open-label			
Subject group type	Reporting group			
Number of subjects analysed	336[2]			
Units: Spearman Correlation Coefficient				
number (confidence interval 95%)				
Month 3 / Month 3	0.169 (0.060 to 0.274)			
Month 3 / Month 6	0.245 (0.130 to 0.353)			
Month 3 / Month 9	0.274 (0.160 to 0.380)			
Month 3 / Month 12	0.178 (0.060 to 0.290)			
Month 6 / Month 6	0.258 (0.144 to 0.365)			
Month 6 / Month 9	0.322 (0.209 to 0.426)			
Month 6 / Month 12	0.274 (0.158 to 0.382)			
Month 9 / Month 9	0.343 (0.234 to 0.444)			
Month 9 / Month 12	0.332 (0.221 to 0.434)			
Month 12 / Month 12	0.266 (0.155 to 0.370)			

Notes:

[2] - The value is the number of subjects in baseline visit.

Statistical analyses

No statistical analyses for this end point

Primary: The correlation CFS score and SANDE symptoms score in Period 2

End point title	The correlation CFS score and SANDE symptoms score in Period 2[3]

End point description:

The primary efficacy endpoint is the correlation between change from baseline in CFS score and SANDE symptoms score at each visit, and cross correlation of sign at visit X versus symptoms at visit X+i, if any.

End point type	Primary

End point timeframe:

Baseline visit (Month 12), Month 15, Month 18, Month 21,Month 24, Month 27, Month 30,Month 33, Month 36

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical testing was conducted for this item measures in this study.

End point values	Masked Ikervis	Masked Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[4]	97[5]		
Units: Spearman Correlation Coefficient				
number (confidence interval 95%)				
Month 15 / Month 15	0.181 (0.020 to 0.333)	0.059 (-0.143 to 0.257)		
Month 15 / Month 18	0.282 (0.123 to 0.427)	-0.131 (-0.329 to 0.078)		
Month 15 / Month 21	0.119 (-0.049 to 0.280)	-0.122 (-0.323 to 0.090)		
Month 15 / Month 24	0.126 (-0.040 to 0.286)	-0.014 (-0.222 to 0.195)		
Month 15 / Month 27	0.182 (0.015 to 0.339)	-0.050 (-0.257 to 0.161)		
Month 15 / Month 30	0.073 (-0.097 to 0.239)	0.028 (-0.184 to 0.237)		
Month 15 / Month 33	0.141 (-0.028 to 0.302)	-0.110 (-0.314 to 0.105)		
Month 15 / Month 36	0.242 (0.076 to 0.395)	-0.049 (-0.259 to 0.166)		
Month 18 / Month 18	0.264 (0.103 to 0.411)	0.152 (-0.058 to 0.350)		
Month 18 / Month 21	0.248 (0.084 to 0.399)	0.129 (-0.086 to 0.331)		
Month 18 / Month 24	0.130 (-0.039 to 0.291)	0.109 (-0.105 to 0.314)		
Month 18 / Month 27	0.196 (0.027 to 0.354)	0.038 (-0.175 to 0.248)		
Month 18 / Month 30	0.179 (0.008 to 0.339)	0.069 (-0.146 to 0.278)		

Month 18 / Month 33	0.237 (0.070 to 0.392)	0.077 (-0.140 to 0.287)		
Month 18 / Month 36	0.282 (0.117 to 0.432)	0.053 (-0.165 to 0.265)		
Month 21 / Month 21	0.222 (0.058 to 0.374)	0.184 (-0.026 to 0.377)		
Month 21 / Month 24	0.157 (-0.009 to 0.315)	0.027 (-0.183 to 0.234)		
Month 21 / Month 27	0.243 (0.079 to 0.395)	0.115 (-0.096 to 0.317)		
Month 21 / Month 30	0.245 (0.079 to 0.397)	0.078 (-0.135 to 0.284)		
Month 21 / Month 33	0.227 (0.061 to 0.381)	0.053 (-0.160 to 0.262)		
Month 21 / Month 36	0.271 (0.107 to 0.421)	0.144 (-0.071 to 0.346)		
Month 24 / Month 24	0.267 (0.105 to 0.415)	0.101 (-0.110 to 0.303)		
Month 24 / Month 27	0.301 (0.140 to 0.447)	0.094 (-0.118 to 0.298)		
Month 24 / Month 30	0.192 (0.023 to 0.350)	0.015 (-0.197 to 0.225)		
Month 24 / Month 33	0.281 (0.118 to 0.430)	0.085 (-0.129 to 0.291)		
Month 24 / Month 36	0.297 (0.134 to 0.444)	0.127 (-0.088 to 0.331)		
Month 27 / Month 27	0.292 (0.132 to 0.438)	0.110 (-0.101 to 0.311)		
Month 27 / Month 30	0.249 (0.084 to 0.401)	0.140 (-0.072 to 0.339)		
Month 27 / Month 33	0.218 (0.052 to 0.372)	0.191 (-0.021 to 0.386)		
Month 27 / Month 36	0.284 (0.122 to 0.432)	0.220 (0.009 to 0.413)		
Month 30 / Month 30	0.346 (0.188 to 0.487)	0.135 (-0.076 to 0.335)		
Month 30 / Month 33	0.187 (0.019 to 0.345)	0.142 (-0.071 to 0.343)		
Month 30 / Month 36	0.315 (0.153 to 0.460)	0.216 (0.004 to 0.409)		
Month 33 / Month 33	0.248 (0.084 to 0.399)	0.193 (-0.018 to 0.388)		
Month 33 / Month 36	0.293 (0.131 to 0.440)	0.163 (-0.051 to 0.362)		
Month 36 / Month 36	0.384 (0.231 to 0.519)	0.264 (0.055 to 0.451)		

Notes:

[4] - The value is the number of subjects in baseline visit.

[5] - The value is the number of subjects in baseline visit.

Statistical analyses

No statistical analyses for this end point

Primary: The correlation CFS score and SANDE symptoms score Entire Study

End point title	The correlation CFS score and SANDE symptoms score Entire Study[6]

End point description:

End point type	Primary

End point timeframe:

Baseline visit, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21,Month 24, Month 27, Month 30,Month 33, and Month 36

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical testing was conducted for this item measures in this study.

End point values	Masked Ikervis	Masked Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[7]	97[8]		
Units: Spearman Correlation Coefficient				
number (confidence interval 95%)				
Month 3 / Month 3	0.159 (-0.006 to 0.316)	0.097 (-0.110 to 0.296)		
Month 3 / Month 6	0.124 (-0.047 to 0.288)	0.254 (0.046 to 0.441)		
Month 3 / Month 9	0.278 (0.117 to 0.426)	0.100 (-0.110 to 0.302)		
Month 3 / Month 12	0.184 (0.019 to 0.339)	0.028 (-0.178 to 0.232)		
Month 3 / Month 15	0.241 (0.078 to 0.391)	0.103 (-0.104 to 0.301)		
Month 3 / Month 18	0.165 (-0.004 to 0.325)	0.026 (-0.187 to 0.236)		
Month 3 / Month 21	0.154 (-0.016 to 0.316)	-0.041 (-0.253 to 0.175)		
Month 3 / Month 24	0.074 (-0.096 to 0.241)	0.066 (-0.150 to 0.275)		
Month 3 / Month 27	0.107 (-0.064 to 0.272)	0.045 (-0.171 to 0.257)		
Month 3 / Month 30	0.179 (0.008 to 0.339)	-0.003 (-0.217 to 0.212)		
Month 3 / Month 33	0.183 (0.012 to 0.343)	-0.013 (-0.228 to 0.203)		
Month 3 / Month 36	0.052 (-0.121 to 0.221)	0.092 (-0.128 to 0.303)		
Month 6 / Month 6	0.173 (0.006 to 0.331)	0.286 (0.083 to 0.466)		
Month 6 / Month 9	0.312 (0.150 to 0.457)	0.240 (0.031 to 0.429)		
Month 6 / Month 12	0.222 (0.056 to 0.376)	0.220 (0.012 to 0.409)		
Month 6 / Month 15	0.296 (0.135 to 0.441)	0.205 (-0.003 to 0.396)		
Month 6 / Month 18	0.282 (0.118 to 0.432)	0.230 (0.016 to 0.423)		
Month 6 / Month 21	0.304 (0.139 to 0.453)	0.090 (-0.129 to 0.300)		
Month 6 / Month 24	0.322 (0.159 to 0.467)	0.133 (-0.084 to 0.338)		
Month 6 / Month 27	0.314 (0.149 to 0.462)	0.117 (-0.101 to 0.325)		
Month 6 / Month 30	0.223 (0.050 to 0.383)	0.162 (-0.057 to 0.366)		
Month 6 / Month 33	0.205 (0.032 to 0.366)	0.140 (-0.081 to 0.348)		
Month 6 / Month 36	0.201 (0.027 to 0.363)	0.245 (0.026 to 0.441)		

Month 9 / Month 9	0.288 (0.127 to 0.434)	0.300 (0.099 to 0.478)		
Month 9 / Month 12	0.186 (0.019 to 0.342)	0.333 (0.135 to 0.505)		
Month 9 / Month 15	0.366 (0.211 to 0.503)	0.357 (0.161 to 0.525)		
Month 9 / Month 18	0.382 (0.227 to 0.519)	0.325 (0.124 to 0.500)		
Month 9 / Month 21	0.286 (0.120 to 0.436)	0.277 (0.068 to 0.463)		
Month 9 / Month 24	0.227 (0.058 to 0.384)	0.333 (0.130 to 0.510)		
Month 9 / Month 27	0.211 (0.039 to 0.371)	0.340 (0.135 to 0.516)		
Month 9 / Month 30	0.211 (0.051 to 0.383)	0.367 (0.165 to 0.540)		
Month 9 / Month 33	0.293 (0.125 to 0.445)	0.284 (0.071 to 0.472)		
Month 9 / Month 36	0.240 (0.068 to 0.398)	0.461 (0.270 to 0.617)		
Month 12 / Month 12	0.160 (-0.001 to 0.314)	0.174 (-0.027 to 0.361)		
Month 12 / Month 15	0.266 (0.109 to 0.411)	0.175 (-0.025 to 0.362)		
Month 12 / Month 18	0.309 (0.152 to 0.451)	0.259 (0.056 to 0.441)		
Month 12 / Month 21	0.196 (0.031 to 0.351)	0.100 (-0.111 to 0.302)		
Month 12 / Month 24	0.185 (0.021 to 0.340)	0.178 (-0.030 to 0.371)		
Month 12 / Month 27	0.214 (0.048 to 0.368)	0.161 (-0.049 to 0.358)		
Month 12 / Month 30	0.239 (0.073 to 0.391)	0.203 (-0.006 to 0.396)		
Month 12 / Month 33	0.231 (0.066 to 0.384)	0.178 (-0.034 to 0.374)		
Month 12 / Month 36	0.195 (0.027 to 0.352)	0.250 (0.040 to 0.439)		
Month 15 / Month 15	0.331 (0.178 to 0.468)	0.427 (0.247 to 0.578)		
Month 15 / Month 18	0.384 (0.234 to 0.516)	0.387 (0.195 to 0.550)		
Month 15 / Month 21	0.246 (0.083 to 0.397)	0.257 (0.051 to 0.443)		
Month 15 / Month 24	0.260 (0.099 to 0.408)	0.380 (0.187 to 0.545)		
Month 15 / Month 27	0.298 (0.137 to 0.444)	0.381 (0.187 to 0.547)		
Month 15 / Month 30	0.335 (0.176 to 0.477)	0.406 (0.214 to 0.568)		
Month 15 / Month 33	0.343 (0.186 to 0.484)	0.358 (0.158 to 0.529)		
Month 15 / Month 36	0.347 (0.189 to 0.487)	0.453 (0.266 to 0.608)		
Month 18 / Month 18	0.450 (0.307 to 0.572)	0.469 (0.289 to 0.617)		
Month 18 / Month 21	0.389 (0.237 to 0.523)	0.374 (0.176 to 0.543)		
Month 18 / Month 24	0.276 (0.113 to 0.424)	0.458 (0.272 to 0.610)		
Month 18 / Month 27	0.326 (0.165 to 0.469)	0.414 (0.222 to 0.575)		

Month 18 / Month 30	0.412 (0.260 to 0.545)	0.474 (0.290 to 0.624)		
Month 18 / Month 33	0.413 (0.261 to 0.545)	0.422 (0.228 to 0.583)		
Month 18 / Month 36	0.422 (0.270 to 0.553)	0.532 (0.357 to 0.670)		
Month 21 / Month 21	0.357 (0.204 to 0.494)	0.328 (0.128 to 0.502)		
Month 21 / Month 24	0.306 (0.147 to 0.449)	0.351 (0.154 to 0.521)		
Month 21 / Month 27	0.340 (0.183 to 0.480)	0.395 (0.202 to 0.558)		
Month 21 / Month 30	0.357 (0.201 to 0.496)	0.380 (0.184 to 0.547)		
Month 21 / Month 33	0.330 (0.172 to 0.472)	0.356 (0.155 to 0.528)		
Month 21 / Month 36	0.354 (0.197 to 0.493)	0.493 (0.313 to 0.639)		
Month 24 / Month 24	0.410 (0.261 to 0.540)	0.429 (0.243 to 0.585)		
Month 24 / Month 27	0.395 (0.243 to 0.528)	0.401 (0.209 to 0.563)		
Month 24 / Month 30	0.361 (0.204 to 0.500)	0.388 (0.193 to 0.553)		
Month 24 / Month 33	0.392 (0.239 to 0.526)	0.402 (0.207 to 0.565)		
Month 24 / Month 36	0.422 (0.271 to 0.552)	0.499 (0.320 to 0.644)		
Month 27 / Month 27	0.287 (0.126 to 0.433)	0.260 (0.055 to 0.445)		
Month 27 / Month 30	0.311 (0.151 to 0.456)	0.322 (0.121 to 0.498)		
Month 27 / Month 33	0.243 (0.079 to 0.395)	0.319 (0.116 to 0.496)		
Month 27 / Month 36	0.283 (0.120 to 0.431)	0.423 (0.231 to 0.582)		
Month 30 / Month 30	0.414 (0.264 to 0.545)	0.455 (0.271 to 0.607)		
Month 30 / Month 33	0.272 (0.108 to 0.422)	0.411 (0.219 to 0.572)		
Month 30 / Month 36	0.363 (0.206 to 0.502)	0.515 (0.341 to 0.656)		
Month 33 / Month 33	0.318 (0.159 to 0.461)	0.447 (0.261 to 0.601)		
Month 33 / Month 36	0.354 (0.197 to 0.493)	0.447 (0.260 to 0.602)		
Month 36 / Month 36	0.484 (0.343 to 0.603)	0.521 (0.348 to 0.660)		

Notes:

[7] - The value is the number of subjects in baseline visit.

[8] - The value is the number of subjects in baseline visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Corneal Fluorescein Staining (CFS) Score in each Visit in Period 1

End point title	Corneal Fluorescein Staining (CFS) Score in each Visit in Period 1

End point description:

End point type	Secondary

End point timeframe:

Baseline visit, Month 3, Month 6, Month 9 and Month 12

End point values	Open-label			
Subject group type	Reporting group			
Number of subjects analysed	336[9]			
Units: CFS Score				
arithmetic mean (standard error)				
Baseline	3.62 (± 0.667)			
Month 3	2.24 (± 1.072)			
Month 6	1.72 (± 1.137)			
Month 9	1.42 (± 1.094)			
Month 12	1.14 (± 1.008)			

Notes:

[9] - The value is the number of subjects in baseline visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline by Visit for Corneal Fluorescein Staining (CFS) Score in Period 1

End point title	Change From Baseline by Visit for Corneal Fluorescein Staining (CFS) Score in Period 1

End point description:

End point type	Secondary

End point timeframe:

Baseline visit, Month 3, Month 6, Month 9 and Month 12

End point values	Open-label			
Subject group type	Reporting group			
Number of subjects analysed	336[10]			
Units: CFS Score				
arithmetic mean (standard error)				
Month 3	-1.38 (± 0.995)			
Month 6	-1.91 (± 1.143)			
Month 9	-2.20 (± 1.123)			
Month 12	-2.49 (± 0.981)			

Notes:

[10] - Baseline number.

Statistical analyses

No statistical analyses for this end point

Secondary: Corneal Fluorescein Staining (CFS) Score in each Visit in Period 2

End point title	Corneal Fluorescein Staining (CFS) Score in each Visit in Period 2

End point description:

End point type	Secondary

End point timeframe:

Baseline visit (Month 12), Month 15, Month 18, Month 21,Month 24, Month 27, Month 30,Month 33, and Month 36

End point values	Masked Ikervis	Masked Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[11]	97[12]		
Units: CFS score				
arithmetic mean (standard error)				
Baseline visit (Month 12)	0.91 (± 0.731)	0.86 (± 0.684)		
Month 15	0.95 (± 0.871)	1.06 (± 1.083)		
Month 18	1.00 (± 1.019)	1.04 (± 0.939)		
Month 21	0.93 (± 0.881)	0.83 (± 0.754)		
Month 24	0.99 (± 0.980)	0.90 (± 0.947)		
Month 27	0.80 (± 0.836)	0.95 (± 0.977)		
Month 30	0.86 (± 0.884)	0.83 (± 0.937)		
Month 33	0.86 (± 0.931)	0.89 (± 1.088)		
Month 36	0.87 (± 0.978)	0.81 (± 1.044)		

Notes:

[11] - The value is the number of subjects in baseline visit.

[12] - The value is the number of subjects in baseline visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline by Visit for Corneal Fluorescein Staining (CFS) Score in Period 2

End point title	Change From Baseline by Visit for Corneal Fluorescein Staining (CFS) Score in Period 2

End point description:

End point type	Secondary

End point timeframe:

Baseline visit (Month 12), Month 15, Month 18, Month 21,Month 24, Month 27, Month 30,Month 33, and Month 36

End point values	Masked Ikervis	Masked Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[13]	97[14]		
Units: CFS Score				
arithmetic mean (standard error)				
Month 15	-0.05 (± 0.068)	0.10 (± 0.083)		
Month 18	-0.01 (± 0.074)	0.12 (± 0.090)		
Month 21	-0.07 (± 0.067)	-0.07 (± 0.082)		
Month 24	-0.02 (± 0.077)	0.04 (± 0.094)		
Month 27	-0.19 (± 0.073)	0.06 (± 0.090)		
Month 30	-0.12 (± 0.075)	-0.05 (± 0.092)		
Month 33	-0.13 (± 0.079)	0.02 (± 0.098)		
Month 36	-0.12 (± 0.082)	-0.05 (± 0.101)		

Notes:

[13] - Baseline number.

[14] - Baseline number.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Incidence and severity of ocular and systemic adverse events (AEs) over the three-year study period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Period 1: Open-Label
Reporting group description: -	
Reporting group title	Period 2: Masked Ikervis
Reporting group description: -	
Reporting group title	Period 2: Masked Vehicle
Reporting group description: -	

Serious adverse events	Period 1: Open-Label	Period 2: Masked Ikervis	Period 2: Masked Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 344 (4.36%)	12 / 147 (8.16%)	9 / 97 (9.28%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0		0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			

subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery bypass			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital prolapse			

subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain stem stroke			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior capsule opacification			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 344 (1.16%)	2 / 147 (1.36%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sialoadenitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	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	Period 1: Open-Label	Period 2: Masked Ikervis	Period 2: Masked Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 344 (40.12%)	58 / 147 (39.46%)	39 / 97 (40.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eyelid haemangioma			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal lymphoma			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Varicose ulceration			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Arteriosclerosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Lens extraction			
subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	0	2	0
Cataract operation			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Hip surgery			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Foot operation			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Instillation site pain			
subjects affected / exposed	3 / 344 (0.87%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Instillation site paraesthesia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Product intolerance			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Discomfort			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Seasonal allergy			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Metrorrhagia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Endometrial hyperplasia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Asthma			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Dyspnoea			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pharyngeal oedema			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Vocal cord inflammation			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Investigations			
Blood cholesterol			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Blood pressure decreased			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Body temperature increased			

subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Vital dye staining cornea present			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Foreign body in eye			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
Animal bite			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Soft tissue foreign body			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Tendon rupture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Accidental overdose			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Atrial fibrillation			

subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Coronary artery stenosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Facial neuralgia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Migraine with aura			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Vertigo			

subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Eye irritation			
subjects affected / exposed	26 / 344 (7.56%)	4 / 147 (2.72%)	0 / 97 (0.00%)
occurrences (all)	28	4	0
Eye pain			
subjects affected / exposed	16 / 344 (4.65%)	0 / 147 (0.00%)	2 / 97 (2.06%)
occurrences (all)	18	0	2
Dry eye			
subjects affected / exposed	15 / 344 (4.36%)	3 / 147 (2.04%)	5 / 97 (5.15%)
occurrences (all)	15	3	5
Eye pruritus			
subjects affected / exposed	12 / 344 (3.49%)	3 / 147 (2.04%)	1 / 97 (1.03%)
occurrences (all)	12	4	1
Ocular hyperaemia			
subjects affected / exposed	11 / 344 (3.20%)	3 / 147 (2.04%)	0 / 97 (0.00%)
occurrences (all)	11	3	0
Visual acuity reduced			
subjects affected / exposed	4 / 344 (1.16%)	3 / 147 (2.04%)	3 / 97 (3.09%)
occurrences (all)	5	4	3
Conjunctival hyperaemia			
subjects affected / exposed	4 / 344 (1.16%)	1 / 147 (0.68%)	2 / 97 (2.06%)
occurrences (all)	4	1	2
Lacrimation increased			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	4	1	1
Vision blurred			
subjects affected / exposed	4 / 344 (1.16%)	3 / 147 (2.04%)	1 / 97 (1.03%)
occurrences (all)	4	3	1
Abnormal sensation in eye			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	3	1	1
Chalazion			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	2 / 97 (2.06%)
occurrences (all)	3	2	2

Conjunctival oedema			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	3	1	1
Ocular discomfort			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	3	1	0
Blepharospasm			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Corneal leukoma			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Corneal oedema			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Eyelid oedema			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	2	1	1
Eyelids pruritus			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
Foreign body sensation in eyes			
subjects affected / exposed	2 / 344 (0.58%)	3 / 147 (2.04%)	2 / 97 (2.06%)
occurrences (all)	2	3	2
Keratitis			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	2 / 97 (2.06%)
occurrences (all)	2	1	2
Lenticular opacities			
subjects affected / exposed	2 / 344 (0.58%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	2	2	0
Meibomian gland dysfunction			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	2	1	1
Noninfective conjunctivitis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1

Photophobia			
subjects affected / exposed	2 / 344 (0.58%)	3 / 147 (2.04%)	1 / 97 (1.03%)
occurrences (all)	2	3	1
Blepharitis			
subjects affected / exposed	1 / 344 (0.29%)	5 / 147 (3.40%)	3 / 97 (3.09%)
occurrences (all)	1	5	5
Cataract			
subjects affected / exposed	1 / 344 (0.29%)	5 / 147 (3.40%)	0 / 97 (0.00%)
occurrences (all)	1	6	0
Conjunctivitis allergic			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Dacryolith			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Dermatochalasis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Eczema eyelids			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Erythema of eyelid			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	1	1	1
Lacrimation disorder			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Ocular hypertension			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pinguecula			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Lacrimal disorder			
subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	2 / 97 (2.06%)
occurrences (all)	0	3	3

Posterior capsule opacification			
subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	2 / 97 (2.06%)
occurrences (all)	0	2	2
Corneal degeneration			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Episcleritis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Eye allergy			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Meibomianitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Eyelash discolouration			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Macular cyst			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Meibomian gland discharge			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Photopsia			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1

Retinal degeneration			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Trichiasis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	2	1	0
Food poisoning			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 344 (0.29%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	1	2	0
Hand dermatitis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Dandruff			

subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Renal cyst			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 344 (1.16%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	4	2	0
Arthralgia			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	2	1	1
Fibromyalgia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Rheumatoid arthritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			

subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	0	2	0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Foot deformity			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Meniscal degeneration			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Plantar fasciitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Infections and infestations			
COVID-19			
subjects affected / exposed	8 / 344 (2.33%)	10 / 147 (6.80%)	5 / 97 (5.15%)
occurrences (all)	8	11	5
Conjunctivitis			
subjects affected / exposed	4 / 344 (1.16%)	3 / 147 (2.04%)	2 / 97 (2.06%)
occurrences (all)	5	4	2
Nasopharyngitis			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	4	1	0
Hordeolum			
subjects affected / exposed	3 / 344 (0.87%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	3	3	1
Bronchitis			
subjects affected / exposed	2 / 344 (0.58%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1

Herpes zoster			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
Viral infection			
subjects affected / exposed	2 / 344 (0.58%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	2	1	0
Asymptomatic COVID-19			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Eye infection viral			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Eyelid infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 344 (0.29%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	1	2	0
Tooth abscess			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	1 / 344 (0.29%)	2 / 147 (1.36%)	1 / 97 (1.03%)
occurrences (all)	1	2	1
Wound infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 147 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 344 (0.00%)	2 / 147 (1.36%)	0 / 97 (0.00%)
occurrences (all)	0	2	0

Pharyngitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
COVID-19 pneumonia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Herpes ophthalmic			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Lyme disease			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	0 / 344 (0.00%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Borrelia infection			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Parotitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Postoperative wound infection			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1

Suspected COVID-19			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 344 (0.00%)	0 / 147 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 344 (0.29%)	1 / 147 (0.68%)	0 / 97 (0.00%)
occurrences (all)	1	1	0

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