Clinical trial results:
A Clinical Study to Assess the Efficacy and Onset of Pain Relief of Topical MFC51123 Diclofenac-Menthol Gel versus Controls in Ankle Sprain

Summary

EudraCT number	2013-000992-33
Trial protocol	DE
Global end of trial date	22 March 2015

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	14 July 2016

Trial information

Trial identification

Sponsor protocol code	RH01805

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlakosmithKline
Sponsor organisation address	1500 Littleton Road, Parsippany, United States, NJ 07054
Public contact	GSK CH Clinical Trials, GlaxoSmithKline Consumer Healthcare, +44 1932826987, rd.gskch-clinical-trials@gsk.com
Scientific contact	GSK CH Clinical Trials, GlaxoSmithKline Consumer Healthcare, +44 1932826987, rd.gskch-clinical-trials@gsk.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	12 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of MFC51123 gel over placebo as measured by Area Under the Curve of Pain Intensity on Movement (walking 5 steps on flat surface) for the period from 24 to 72 hours of treatment (AUC1-3days).

Protection of trial subjects:

The study was conducted according to the ethical principles of the Declaration of Helsinki.
The study drug was to be discontinued if continuing would result in a significant safety risk for the subject as per the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
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	Germany: 385
Worldwide total number of subjects	385
EEA total number of subjects	385

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)	13
Adults (18-64 years)	372
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 16 centers in the Germany.

Pre-assignment

Screening details:

The study population consisted of a representative group of male and female subjects aged minimum of 16 years and maximum of 63 years suffering from ankle sprain. Of the 388 subjects screened, 385 were randomized in the study.

Period 1

Period 1 title	Overall Study (overall period)
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	Diclofenac plus(+) Menthol

Arm description:

1% Diclofenac sodium and 3% menthol gel was supplied in 30 gram (g) tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.

Arm type	Experimental
Investigational medicinal product name	1% diclofenac sodium+ 3% menthol gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects were instructed to apply approximately 4 grams of the assigned topical gel product 4 times daily to the injured ankle. The subject were instructed to fill the circle on a the Gel Strip, a 90mm x 50mm piece of glycine paper designed to gauge the amount of gel to apply for a single dose.

Arm title	Diclofenac

Arm description:

1% Diclofenac sodium + 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.

Arm type	Experimental
Investigational medicinal product name	1% diclofenac sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects were instructed to apply approximately 4 grams of the assigned topical gel product 4 times daily to the injured ankle. The subject were instructed to fill the circle on a the Gel Strip, a 90mm x 50mm piece of glycine paper designed to gauge the amount of gel to apply for a single dose.

Arm title	Menthol

Arm description:

3% menthol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.

Arm type	Active comparator

Investigational medicinal product name	3% menthol gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects were instructed to apply approximately 4 grams of the assigned topical gel product 4 times daily to the injured ankle. The subject were instructed to fill the circle on a the Gel Strip, a 90mm x 50mm piece of glycine paper designed to gauge the amount of gel to apply for a single dose.

Arm title	Placebo

Arm description:

Placebo with 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects were instructed to apply approximately 4 grams of the assigned topical gel product 4 times daily to the injured ankle. The subject were instructed to fill the circle on a the Gel Strip, a 90mm x 50mm piece of glycine paper designed to gauge the amount of gel to apply for a single dose.

Number of subjects in period 1	Diclofenac plus(+) Menthol	Diclofenac	Menthol
Started	118	113	78
Completed	105	106	74
Not completed	13	7	4
Consent withdrawn by subject	-	1	1
Protocol violation	-	1	-
Other Reason	2	2	-
Adverse Events	10	3	3
Lost to follow-up	1	-	-

Number of subjects in period 1	Placebo
Started	76
Completed	75
Not completed	1
Consent withdrawn by subject	-
Protocol violation	1
Other Reason	-
Adverse Events	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Diclofenac plus(+) Menthol
Reporting group description:	
1% Diclofenac sodium and 3% menthol gel was supplied in 30 gram (g) tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Diclofenac
Reporting group description:	
1% Diclofenac sodium + 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Menthol
Reporting group description:	
3% menthol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo with 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	

Reporting group values	Diclofenac plus(+) Menthol	Diclofenac	Menthol
Number of subjects	118	113	78
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 32.3 ± 11.82	 32.2 ± 11.43	 33.7 ± 12.09
Gender categorical Units: Subjects			
Female	50	41	39
Male	68	72	39

Reporting group values	Placebo	Total	
Number of subjects	76	385	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 33 ± 11.61	 -	
Gender categorical Units: Subjects			
Female	36	166	
Male	40	219	

End points

End points reporting groups

Reporting group title	Diclofenac plus(+) Menthol
Reporting group description:	
1% Diclofenac sodium and 3% menthol gel was supplied in 30 gram (g) tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Diclofenac
Reporting group description:	
1% Diclofenac sodium + 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Menthol
Reporting group description:	
3% menthol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo with 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	

Primary: Area Under the Curve from Day 1 to Day 3 (AUC1-3 days) of Pain Intensity (PI) on Movement for Diclofenac/Methanol gel and Placebo gel

End point title	Area Under the Curve from Day 1 to Day 3 (AUC1-3 days) of Pain Intensity (PI) on Movement for Diclofenac/Methanol gel and Placebo gel[1]
End point description:	
AUC of pain intensity (PI) on movement was measured by numerical rating scale (NRS) during the 48 hour time interval from Day 1 to 3. AUC1-3 day was calculated based on trapezoidal method. PI was measured in NRS scale from 0 (no pain) to 10 (extreme pain). Subjects assessed the severity of ankle pain using NRS scale at baseline (prior to treatment) and at 10, 30 minutes and 1, 4, 6, 12, 18 and 24 hours after the first dose of treatment and twice daily after dosing.	
End point type	Primary
End point timeframe:	
Upto 72 hours	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint required the descriptive and statistical data for Diclofenac/Methanol gel and Placebo gel only, not for all the treatments group involved in this study.

End point values	Diclofenac plus(+)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	75		
Units: Score on scale				
arithmetic mean (standard deviation)	276.97 (± 111.356)	282.88 (± 100.958)		

Statistical analyses

Statistical analysis title	1% Diclofenac sodium (sod.) +3% Menthol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4144
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-9.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.45
upper limit	12.98

Secondary: Pain Intensity Difference (PID) on Movement

End point title	Pain Intensity Difference (PID) on Movement

End point description:

PID on movement (after walking 5 steps on a flat surface), calculated as PI at a given time 't' subtracted by the PI at baseline, measured on movement using NRS scale. Participants assessed the severity of ankle pain using the NRS scale at baseline (prior to treatment) and at 10, 30 minutes (min.) and 1, 4, 6, 12, 18 and 24 hours after the first dose of treatment and twice daily after dosing. ITT population included all participants who fulfilled all the study entry criteria, received the study treatment and had at least one post-baseline efficacy assessment. This analysis was conducted on ITT population.

End point type	Secondary

End point timeframe:

Baseline to 10 days

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on scale				
arithmetic mean (standard deviation)				
At Baseline (117, 112, 77, 75)	7.8 (± 1.55)	7.4 (± 1.44)	7.8 (± 1.6)	7.7 (± 1.47)
At 10 min. (117, 112, 77, 75)	7.54 (± 1.808)	7.23 (± 1.571)	7.47 (± 1.854)	7.37 (± 1.6)
At 30 min. (117, 112, 77, 75)	7.33 (± 1.974)	7.06 (± 1.689)	7.26 (± 1.852)	7.15 (± 1.706)
At 1 hour (117, 112, 77, 75)	7.21 (± 2.05)	6.92 (± 1.761)	7.12 (± 2.039)	7.05 (± 1.8)
At 4 hour (117, 112, 77, 75)	7.06 (± 2.147)	6.94 (± 1.802)	6.96 (± 2.112)	7 (± 1.748)
At 6 hour (117, 112, 77, 75)	6.98 (± 2.141)	6.75 (± 1.758)	6.84 (± 2.213)	6.83 (± 1.855)
At 12 hour (117, 112, 77, 75)	6.93 (± 2.148)	6.43 (± 1.93)	6.58 (± 2.347)	6.75 (± 2.08)
At 18 hour (117, 112, 77, 75)	6.58 (± 2.163)	6.1 (± 2.022)	6.31 (± 2.429)	6.53 (± 2.107)
At 24 hour (117, 112, 77, 75)	6.15 (± 2.273)	5.84 (± 2.078)	6 (± 2.487)	6.16 (± 2.137)
At 36 hour (117, 112, 77, 75)	6.18 (± 2.427)	5.77 (± 2.058)	6.21 (± 2.478)	6.37 (± 2.065)
At 48 hour (117, 112, 77, 75)	5.85 (± 2.447)	5.41 (± 2.099)	5.71 (± 2.665)	5.77 (± 2.436)
At 60 hour (117, 112, 77, 75)	5.36 (± 2.398)	5.16 (± 2.192)	5.19 (± 2.616)	5.64 (± 2.21)
At 72 hour (117, 112, 77, 75)	5.22 (± 2.492)	5 (± 2.144)	5.21 (± 2.657)	5.41 (± 2.218)
At 84 hour (113, 107, 75, 75)	4.92 (± 2.342)	4.77 (± 2.108)	4.65 (± 2.549)	5.01 (± 2.293)

At 96 hour (112, 107, 75, 74)	4.64 (± 2.189)	4.67 (± 2.162)	4.71 (± 2.572)	4.88 (± 2.196)
At 108 hour (112, 107, 75, 74)	4.38 (± 2.306)	4.44 (± 2.093)	4.25 (± 2.526)	4.49 (± 2.115)
At 120 hour (111, 107, 74, 74)	4.35 (± 2.131)	4.28 (± 2.145)	4.36 (± 2.594)	4.53 (± 1.995)
At 132 hour (110, 107, 74, 74)	4.03 (± 2.178)	3.92 (± 2.001)	4 (± 2.449)	4.19 (± 2.194)
At 144 hour (110, 107, 74, 74)	3.96 (± 2.209)	3.67 (± 2.05)	4.04 (± 2.551)	4.07 (± 2.179)
At 156 hour (109, 107, 74, 74)	3.54 (± 2.154)	3.4 (± 2.041)	3.77 (± 2.497)	3.78 (± 2.198)
At 168 hour (105, 104, 73, 74)	3.5 (± 2.034)	3.33 (± 1.923)	3.81 (± 2.548)	3.72 (± 2.123)
At 180 hour (105, 104, 73, 72)	3.18 (± 2.129)	2.98 (± 1.961)	3.34 (± 2.341)	3.6 (± 2.046)
At 192 hour (101, 102, 71, 72)	3.18 (± 1.962)	2.85 (± 1.9)	3.56 (± 2.506)	3.46 (± 2.055)
At 204 hour (101, 100, 71, 72)	2.56 (± 1.824)	2.51 (± 1.91)	2.9 (± 2.331)	3.13 (± 2.096)
At 216 hour (95, 100, 69, 72)	2.48 (± 1.85)	2.27 (± 1.89)	2.9 (± 2.177)	2.9 (± 1.944)
At 228 hour (95, 100, 69, 72)	2.06 (± 1.844)	1.86 (± 1.831)	2.49 (± 2.266)	2.67 (± 1.891)
At 240 hour (32, 43, 22, 42)	2.13 (± 2.136)	2 (± 2.204)	1.95 (± 2.058)	2.12 (± 1.626)

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Difference (PID) at Rest

End point title	Pain Intensity Difference (PID) at Rest

End point description:

PID at rest was calculated as PI at a given time 't' at rest subtracted by the PI at baseline measured using NRS scale at baseline (prior to treatment) and at 10, 30 min. and 1, 4, 6, 12, 18 and 24 hours after the first dose of treatment and twice daily after dosing.

End point type	Secondary

End point timeframe:

Baseline to 10 days

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on scale				
arithmetic mean (standard deviation)				
At Baseline (117, 112, 77, 75)	7.8 (± 1.55)	7.4 (± 1.44)	7.8 (± 1.6)	7.7 (± 1.47)
At 10 min. (117, 112, 77, 75)	0.34 (± 1.146)	0.43 (± 1.145)	0.17 (± 0.715)	0.25 (± 1.175)
At 30 min. (117, 112, 77, 75)	0.56 (± 1.185)	0.45 (± 1.314)	0.32 (± 0.818)	0.44 (± 1.328)
At 1 hour (117, 112, 77, 75)	0.64 (± 1.283)	0.62 (± 1.187)	0.48 (± 0.94)	0.41 (± 1.62)
At 4 hour (117, 112, 77, 75)	0.62 (± 1.413)	0.53 (± 1.115)	0.66 (± 1.071)	0.43 (± 1.678)
At 6 hour (117, 112, 77, 75)	0.68 (± 1.473)	0.62 (± 1.18)	0.75 (± 1.183)	0.53 (± 1.554)
At 12 hour (117, 112, 77, 75)	0.76 (± 1.501)	0.86 (± 1.432)	0.9 (± 1.429)	0.68 (± 1.535)
At 18 hour (117, 112, 77, 75)	1.03 (± 1.597)	1.14 (± 1.482)	1.1 (± 1.594)	0.85 (± 1.666)
At 24 hour (117, 112, 77, 75)	1.32 (± 1.579)	1.39 (± 1.448)	1.47 (± 1.535)	1.13 (± 1.711)
At 36 hour (117, 112, 77, 75)	1.2 (± 1.549)	1.32 (± 1.49)	1.22 (± 1.635)	1.09 (± 1.787)
At 48 hour (117, 112, 77, 75)	1.43 (± 1.604)	1.53 (± 1.464)	1.51 (± 1.698)	1.45 (± 1.84)
At 60 hour (117, 112, 77, 75)	1.91 (± 1.603)	1.83 (± 1.593)	1.88 (± 1.747)	1.64 (± 1.893)
At 72 hour (117, 112, 77, 75)	1.91 (± 1.776)	1.91 (± 1.545)	1.86 (± 1.782)	1.76 (± 1.972)

At 84 hour (113, 107, 75, 75)	2.11 (± 1.754)	2.19 (± 1.655)	2.19 (± 1.799)	2.03 (± 1.931)
At 96 hour (112, 107, 75, 74)	2.26 (± 1.79)	2.17 (± 1.707)	2.23 (± 1.721)	2 (± 1.72)
At 108 hour (112, 107, 75, 74)	2.46 (± 1.795)	2.43 (± 1.833)	2.48 (± 1.743)	2.27 (± 1.889)
At 120 hour (111, 107, 74, 74)	2.59 (± 1.836)	2.48 (± 1.75)	2.3 (± 1.856)	2.09 (± 1.917)
At 132 hour (110, 107, 74, 74)	2.76 (± 1.877)	2.78 (± 1.819)	2.68 (± 1.873)	2.49 (± 1.967)
At 144 hour (110, 107, 74, 74)	2.77 (± 1.989)	2.77 (± 1.789)	2.59 (± 1.965)	2.49 (± 1.918)
At 156 hour (109, 107, 74, 74)	3.06 (± 2.011)	3.11 (± 1.755)	2.77 (± 1.884)	2.65 (± 2.129)
At 168 hour (105, 104, 73, 74)	3.08 (± 2.037)	3.15 (± 1.805)	2.75 (± 1.869)	2.64 (± 2.004)
At 180 hour (105, 104, 73, 72)	3.37 (± 2.1)	3.38 (± 1.871)	2.95 (± 1.747)	2.88 (± 2.103)
At 192 hour (101, 102, 71, 72)	3.38 (± 2.24)	3.3 (± 2.067)	2.9 (± 1.928)	3 (± 2.035)
At 204 hour (101, 100, 71, 72)	3.67 (± 2.25)	3.61 (± 2.03)	3.37 (± 1.853)	3.21 (± 2.021)
At 216 hour (95, 100, 69, 72)	3.77 (± 2.372)	3.87 (± 2.028)	3.22 (± 2.306)	3.26 (± 1.936)
At 228 hour (95, 100, 69, 72)	4.09 (± 2.348)	4.02 (± 2.074)	3.64 (± 2)	3.53 (± 2.083)
At 240 hour (32, 43, 22, 42)	3.94 (± 2.862)	4.23 (± 2.01)	3.36 (± 2.61)	3.67 (± 2.149)

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Relief Score (PRS)

End point title	Pain Relief Score (PRS)

End point description:

PRS was measured at each time point using a 5-point Pain Relief Scale ranging from 0-4 while at rest (where: 0- No pain relief; 1-a little or perceptible pain relief; 2- meaningful pain relief; 3- a lot of relief; 4- complete relief). Subjects assessed the degree of ankle pain relief using the PRS scores at 10, 30 min. and 1, 4, 6, 12, 18 and 24 hours after the first dose of treatment and twice daily after the first day of treatment.

End point type	Secondary

End point timeframe:

Day 1 to Day 7

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on scale				
arithmetic mean (standard deviation)				
At 10 min. (117, 111, 77, 74)	0.33 (± 0.616)	0.29 (± 0.609)	0.32 (± 0.498)	0.36 (± 0.61)
At 30 min. (117, 111, 77, 75)	0.44 (± 0.635)	0.36 (± 0.585)	0.49 (± 0.599)	0.44 (± 0.683)
At 1 hour (116, 112, 77, 75)	0.48 (± 0.625)	0.46 (± 0.599)	0.57 (± 0.677)	0.4 (± 0.717)
At 4 hour (115, 110, 74, 71)	0.47 (± 0.626)	0.45 (± 0.552)	0.51 (± 0.579)	0.49 (± 0.673)
At 6 hour (109, 105, 70, 69)	0.5 (± 0.603)	0.54 (± 0.605)	0.63 (± 0.618)	0.45 (± 0.607)
At 12 hour (77, 89, 53, 58)	0.6 (± 0.591)	0.72 (± 0.707)	0.74 (± 0.684)	0.62 (± 0.745)
At 18 hour (76, 78, 53, 57)	0.71 (± 0.689)	0.73 (± 0.715)	0.83 (± 0.753)	0.7 (± 0.68)
At 24 hour (111, 105, 72, 72)	0.79 (± 0.662)	0.74 (± 0.68)	0.9 (± 0.754)	0.81 (± 0.642)
At 36 hour (116, 112, 77, 74)	0.84 (± 0.709)	0.84 (± 0.705)	0.88 (± 0.76)	0.78 (± 0.781)
At 48 hour (116, 112, 77, 75)	0.9 (± 0.806)	0.84 (± 0.651)	0.99 (± 0.716)	0.99 (± 0.846)
At 60 hour (115, 111, 77, 75)	1.07 (± 0.78)	1 (± 0.714)	1.16 (± 0.745)	0.96 (± 0.779)

At 72 hour (114, 109, 75, 74)	0.93 (± 0.784)	1.06 (± 0.743)	1.16 (± 0.806)	0.97 (± 0.81)
At 84 hour (113, 106, 75, 75)	1.07 (± 0.81)	1 (± 0.756)	1.25 (± 0.737)	1.11 (± 0.746)
At 96 hour (112, 106, 75, 74)	1.09 (± 0.823)	1.03 (± 0.762)	1.01 (± 0.83)	1.09 (± 0.743)
At 108 hour (111, 105, 75, 74)	1.18 (± 0.876)	1.13 (± 0.809)	1.28 (± 0.894)	1.15 (± 0.734)
At 120 hour (111, 107, 74, 72)	1.11 (± 0.918)	1.14 (± 0.782)	1.24 (± 0.904)	1.1 (± 0.772)
At 132 hour (110, 107, 73, 74)	1.34 (± 0.931)	1.24 (± 0.878)	1.34 (± 0.931)	1.3 (± 0.887)
At 144 hour (110, 107, 74, 73)	1.21 (± 1.015)	1.21 (± 0.919)	1.3 (± 0.947)	1.27 (± 0.886)
At 156 hour (109, 106, 74, 74)	1.41 (± 1.011)	1.3 (± 1.053)	1.47 (± 0.968)	1.32 (± 0.952)
At 168 hour (105, 103, 73, 73)	1.41 (± 1.026)	1.31 (± 0.99)	1.34 (± 1.003)	1.4 (± 0.924)

Statistical analyses

No statistical analyses for this end point

Secondary: Sum of Pain Intensity Difference (SPID)

End point title	Sum of Pain Intensity Difference (SPID)

End point description:

SPID was measured as SPIDt = ∑PIDt x (timet - timet-1) (h) by PID for periods 0-6, 0-12 hours and 0 to 1, 1 to 3 and 0 to 7 days after initial treatment between treatment groups.

End point type	Secondary

End point timeframe:

0-6, 0-12 hours, 0 to 1, 1-3 days, 0-7 days

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
arithmetic mean (standard deviation)				
At 0-6 hours	4.16 (± 9.299)	3.19 (± 5.862)	4.72 (± 6.306)	4.37 (± 8.287)
At 0-12 hours	9.19 (± 18.788)	9.13 (± 13.284)	11.74 (± 14.675)	10.05 (± 16.706)
At 0-1 days	26.01 (± 38.722)	26.54 (± 28.497)	30.91 (± 34.158)	26.21 (± 34.877)
At 1 to 3 days	101.54 (± 87.184)	100.07 (± 71.085)	104.26 (± 83.689)	90.88 (± 82.626)
At 0 to 7 days	451.12 (± 265.919)	452.44 (± 244.488)	464.96 (± 281.243)	438.45 (± 287.369)

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Onset of Pain Relief (TOPR)

End point title	Time of Onset of Pain Relief (TOPR)

End point description: TOPR was measured by the time when subjects reported PRS ≥ 1, i.e. a “little” or “perceptible” pain relief.	
End point type	Secondary
End point timeframe: Baseline to Day 3	

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
median (full range (min-max))	1.03 (0.2 to 157)	4 (0.2 to 168)	1 (0.2 to 94.3)	4 (0.2 to 187.5)

Statistical analyses

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5404
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.48

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs 3% Menthol
Comparison groups	Diclofenac plus(+) Menthol v Menthol
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4639
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.2

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs 1% Diclofenac
Comparison groups	Diclofenac plus(+) Menthol v Diclofenac
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5118
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.43

Secondary: Time of Onset of meaningful Pain Relief (TOMR)	
End point title	Time of Onset of meaningful Pain Relief (TOMR)
End point description:	
TOMR was measured by the time when subjects reported PRS ≥ 2, i.e. "some" or "meaningful" pain relief.	
End point type	Secondary
End point timeframe:	
Baseline to Day 4	

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
median (full range (min-max))	92.5 (0.2 to 203.8)	76.83 (0.2 to 184.1)	72 (0.2 to 203.5)	93.5 (0.2 to 203)

Statistical analyses

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6918
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.31

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs 3% Menthol
Comparison groups	Diclofenac plus(+) Menthol v Menthol
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2389
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.73

Statistical analysis title	1%Diclofenac sod.+3% Menthol vs 1% Diclofenac sod.
Comparison groups	Diclofenac plus(+) Menthol v Diclofenac
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9817
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.37

Secondary: Time of Onset of Cooling Sensation (TOCS)

End point title	Time of Onset of Cooling Sensation (TOCS)

End point description:

Time of onset of cooling sensation was measured by the time when subjects reported to have a 'cooling effect as an enhancement of pain relief'. To assess this endpoint subjects were asked at 10, 30 min. and at 1, 4, 6 hours post first dose "Have you felt a cooling sensation at the injured ankle from the study gel?"

End point type	Secondary

End point timeframe:

Baseline to 6 hours

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
median (full range (min-max))	0.17 (0.17 to 6)	0.17 (0.17 to 6)	0.17 (0.17 to 6)	0.17 (0.17 to 6)

Statistical analyses

Statistical analysis title	1% Diclofenac sod. +3% Menthol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7003
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.43

Statistical analysis title	1% Diclofenac sod.+3% Menthol vs 3% Menthol
Comparison groups	Menthol v Diclofenac plus(+) Menthol
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9565
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.35

Statistical analysis title	1% Diclofenac Sod +3% Menthol vs 1%Diclofenac Sod
Comparison groups	Diclofenac plus(+) Menthol v Diclofenac
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6216
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.4

Secondary: Total Pain Relief (TOTPAR)

End point title	Total Pain Relief (TOTPAR)

End point description:

TOTPAR was calculated as sum of the products of PRS with time interval from one time point to other. Descriptive analysis was provided for each time point.

End point type	Secondary

End point timeframe:

0 - 6, 0 - 12 hours and 0 - 1, 1 - 3, and 0 - 7 days

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
arithmetic mean (standard deviation)				
At 0 - 6 hours	2.81 (± 3.162)	2.64 (± 2.902)	3.27 (± 3.176)	2.75 (± 3.184)
At 0 - 12 hours	6.86 (± 6.125)	6.81 (± 6.178)	8.02 (± 7.045)	6.35 (± 6.732)
At 0 - 1 days	16.04 (± 12.048)	16.14 (± 12.479)	18.85 (± 14.517)	15.71 (± 13.146)
At 1 - 3 days	44.1 (± 29.344)	45.11 (± 26.431)	47.84 (± 29.102)	43.04 (± 31.57)
At 0 - 7 days	172.97 (± 98.838)	170.73 (± 97.187)	184.17 (± 102.787)	174 (± 94.917)

Statistical analyses

No statistical analyses for this end point

Secondary: Skin Temperature

End point title	Skin Temperature

End point description:

Skin temperature was measured by thermal imaging.

End point type	Secondary

End point timeframe:

At 10, 30, 60 minute (min.) and 4 and 6 hours

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	6	6
Units: degree Celsius (°C)				
arithmetic mean (standard deviation)				
At 10 min.	27.69 (± 3.706)	29.31 (± 2.61)	29.92 (± 2.118)	30.93 (± 2.842)
At 30 min.	28.26 (± 3.161)	29.81 (± 2.595)	30.5 (± 2.117)	31.47 (± 3.386)
At 60 min.	28.64 (± 2.986)	30.74 (± 2.781)	30.22 (± 2.388)	31.78 (± 3.213)
At 4 hours	30.52 (± 2.88)	31.26 (± 2.981)	31.15 (± 3.221)	31.57 (± 2.7)
At 6 hours	31.02 (± 2.951)	31.53 (± 3.299)	31.27 (± 3.925)	32.07 (± 3.482)

Statistical analyses

No statistical analyses for this end point

Secondary: Ankle Swelling

End point title	Ankle Swelling

End point description:

Reduction in ankle swelling as change from baseline measured by “figure of eight” method of injured ankle measurement. No overall statistical analyses for this endpoint.

End point type	Secondary

End point timeframe:

Days 1, 3 and 7

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day 1	573.9 (± 57.77)	573.6 (± 50.2)	577.1 (± 55.35)	576.1 (± 50.19)
Day 3	566.2 (± 57.03)	566.9 (± 49.55)	567 (± 56.48)	565.4 (± 52.67)
Day 7	558.3 (± 56.02)	558.8 (± 46.37)	558.4 (± 56.88)	557 (± 50.85)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Recovery

End point title	Time to Complete Recovery

End point description:

Time to complete recovery was measured as the day with complete relief of ankle pain (subject-rated NRS scores were 0 for pain intensity at rest and pain) and swelling (subject did not have any apparent swelling nor experience any pain or limitation of movement of the injured ankle as determined by the Principal Investigator or designee during the course of an ankle exam).

End point type	Secondary

End point timeframe:

Baseline to Day 10

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: score on a scale				
median (full range (min-max))	240 (17 to 240)	240 (48.2 to 240)	240 (53.2 to 240)	240 (145.5 to 240)

Statistical analyses

Statistical analysis title	% Diclofenac Sod+3% Menthol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0408
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	5.7

Statistical analysis title	1% Diclofenac Sod+3% Menthol vs 3% Menthol
Comparison groups	Diclofenac plus(+) Menthol v Menthol
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4507
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.65

Statistical analysis title	1% Diclofenac Sod+3% Menthol vs 1% Diclofenac Sod
Comparison groups	Diclofenac plus(+) Menthol v Diclofenac
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.315
Method	t-test, 2-sided
Parameter estimate	Cox proportional hazard
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.61

Secondary: Patient’s Global Assessment in Response to Treatment (PGART)

End point title	Patient’s Global Assessment in Response to Treatment (PGART)
End point description:	
PGART was measured at the end of study in a scale from 0-4 (where: 0- Poor; 1-Fair; 2- Good; 3-Very Good; 4- Excellent)	
End point type	Secondary
End point timeframe:	
Baseline to Day 10	

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: number of participants				
Poor=0	3	13	6	9
Fair=1	24	20	12	14
Good=2	44	46	26	27
Very Good=3	35	26	26	21
Excellent=4	9	6	5	4

Statistical analyses

Statistical analysis title	Diclofenac Sodium + Methanol vs Placebo
Comparison groups	Diclofenac plus(+) Menthol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1114
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.52

Statistical analysis title	Diclofenac + Methanol vs Methanol
Comparison groups	Diclofenac plus(+) Menthol v Menthol

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5808
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.37

Statistical analysis title	Diclofenac + Methanol vs Diclofenac
Comparison groups	Diclofenac plus(+) Menthol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.55

Secondary: AUC1-3 days of PI on Movement for Diclofenac Sodium + Methanol, Diclofenac, Methanol and Placebo

End point title	AUC1-3 days of PI on Movement for Diclofenac Sodium + Methanol, Diclofenac, Methanol and Placebo

End point description:

AUC of PI on movement was measured by a numerical rating scale (NRS) during the 48 hour time interval from Day 1 to 3. AUC1-3 day was calculated based on trapezoidal method. Pain intensity was measured in NRS scale from 0 (no pain) to 10 (extreme pain). Participants assessed the severity of ankle pain using the NRS scale at baseline (prior to treatment) and at 10, 30 minutes and 1, 4, 6, 12, 18 and 24 hours after the first dose of treatment and twice daily after dosing.

End point type	Secondary

End point timeframe:

Baseline to 72 hours

End point values	Diclofenac plus(+)	Diclofenac	Menthol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	112	77	75
Units: score on a scale				
arithmetic mean (standard deviation)	276.97 (± 111.356)	261.11 (± 96.791)	272.65 (± 118.196)	282.88 (± 100.958)

Statistical analyses

Statistical analysis title	1% diclofenac+3% menthol vs 1% diclofenac
Comparison groups	Diclofenac plus(+) Menthol v Diclofenac
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8761
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.34
upper limit	21.5

Statistical analysis title	1% diclofenac+3% menthol vs 3% menthol
Comparison groups	Diclofenac plus(+) Menthol v Menthol
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8164
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.46
upper limit	24.67

Statistical analysis title	1% diclofenac vs 3% menthol
Comparison groups	Diclofenac v Menthol

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9279
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.27
upper limit	23.33

Statistical analysis title	1% Diclofenac vs Placebo
Comparison groups	Diclofenac v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3442
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-10.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.26
upper limit	11.64

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline upto Day 10 of administration of investigational product	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	0.0

Reporting groups	
Reporting group title	1% Diclofenac plus + 3% Menthol
Reporting group description:	
1% Diclofenac sodium+ 3% menthol gel was supplied in 30 gram (g) tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	1% Diclofenac
Reporting group description:	
1% Diclofenac sodium + 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	3% Menthol
Reporting group description:	
3% menthol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo with 0.09% methanol gel was supplied in 30g tubes for each subject to apply 4g of gel topically to the injured ankle region four times daily for up to 10 days.	

Serious adverse events	1% Diclofenac plus + 3% Menthol	1% Diclofenac	3% Menthol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	0 / 77 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	1% Diclofenac plus + 3% Menthol	1% Diclofenac	3% Menthol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 117 (36.75%)	26 / 112 (23.21%)	22 / 77 (28.57%)
Injury, poisoning and procedural complications			
Arthropod Sting			
subjects affected / exposed	0 / 117 (0.00%)	1 / 112 (0.89%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Skin Abrasion			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Muscle Injury			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 117 (3.42%)	2 / 112 (1.79%)	4 / 77 (5.19%)
occurrences (all)	4	2	4
Hypoaesthesia			
subjects affected / exposed	0 / 117 (0.00%)	1 / 112 (0.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Burning Sensation			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application Site Dryness			
subjects affected / exposed	15 / 117 (12.82%)	7 / 112 (6.25%)	3 / 77 (3.90%)
occurrences (all)	15	7	3
Application site pain			
subjects affected / exposed	7 / 117 (5.98%)	0 / 112 (0.00%)	2 / 77 (2.60%)
occurrences (all)	7	0	2
Application site pruritus			
subjects affected / exposed	5 / 117 (4.27%)	3 / 112 (2.68%)	1 / 77 (1.30%)
occurrences (all)	5	3	1
Application Site Erythema			
subjects affected / exposed	4 / 117 (3.42%)	1 / 112 (0.89%)	2 / 77 (2.60%)
occurrences (all)	4	1	2

Application Site Eczema			
subjects affected / exposed	2 / 117 (1.71%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Application Site Discolouration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Application Site Rash			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Application Site Reaction			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Application Site Vesicles			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Necrosis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Application Site Hypersensitivity			
subjects affected / exposed	0 / 117 (0.00%)	1 / 112 (0.89%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Application Site Burn			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Application Site Swelling			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 117 (0.00%)	1 / 112 (0.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	10 / 117 (8.55%)	10 / 112 (8.93%)	10 / 77 (12.99%)
occurrences (all)	10	10	10
Pruritus			
subjects affected / exposed	7 / 117 (5.98%)	4 / 112 (3.57%)	3 / 77 (3.90%)
occurrences (all)	8	5	3
Erythema			
subjects affected / exposed	6 / 117 (5.13%)	2 / 112 (1.79%)	3 / 77 (3.90%)
occurrences (all)	6	2	3
Blister			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Dermatitis Contact			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin Exfoliation			

subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin Wrinkling			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 117 (0.00%)	1 / 112 (0.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Rash Vesicular			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Skin Reaction			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Back Pain			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Bone Swelling			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Exostosis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 112 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Pyoderma			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 112 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 75 (22.67%)		
Injury, poisoning and procedural complications			
Arthropod Sting			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Skin Abrasion			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Muscle Injury			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		
Hypoaesthesia			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Burning Sensation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application Site Dryness			

subjects affected / exposed	4 / 75 (5.33%)			
occurrences (all)	4			
Application site pain				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences (all)	1			
Application site pruritus				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences (all)	1			
Application Site Erythema				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Eczema				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Discolouration				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Rash				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Reaction				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Vesicles				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Asthenia				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Necrosis				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Hypersensitivity				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences (all)	0			
Application Site Burn				

subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Application Site Swelling			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Blister			

subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Dermatitis			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Dermatitis Contact			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Skin Exfoliation			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Skin Wrinkling			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Rash Vesicular			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Skin Reaction			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Back Pain			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Bone Swelling			

subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Exostosis			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Pyoderma			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	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