Clinical trial results:
A randomized, double-blind, multi-center, placebo-controlled, parallel group study to evaluate the efficacy and safety of an Diclofenac 2% (w/w) cutaneous solution applied twice daily in patients with acute uncomplicated unilateral ankle sprain for a period of 7 consecutive days.
Abbreviated title: Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a diclofenac 2% cutaneous solution vs. placebo in the treatment of acute uncomplicated unilateral ankle sprain

Summary

EudraCT number	2014-005574-11
Trial protocol	DE
Global end of trial date	21 December 2015

Results information

Result version number	v1 (current)
This version publication date	26 December 2018
First version publication date	26 December 2018

Trial information

Trial identification

Sponsor protocol code	Pennsaid-2014/P-3-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Nuvo Pharmaceuticals Inc.
Sponsor organisation address	6733 Mississauga Rd. Suite 610, Mississauga, Canada, ON L5N 6J
Public contact	Bernard Chiasson, Nuvo Pharmaceuticals Inc., +01 905 673 3623, bchiasson@nuvopharm.com
Scientific contact	Christian de Mey, ACPS-Network GmbH, +49611 44762110, c.demey@acps-network.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	08 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2015
Global end of trial reached?	Yes
Global end of trial date	21 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is:
To assess the efficacy of diclofenac sodium 2% w/w cutaneous solution for the treatment of Pain and Inflammation associated with acute soft tissue injury/ankle sprain

Protection of trial subjects:

Patients were monitored throughout participation in the study for occurrence of adverse events after the start of investigational treatment (subjective) and the incidence of abnormal findings in measurements for objective tolerability: vital signs and physical findings

Background therapy:

Paracetamol, 500 mg tablets, were made available by the investigator as non-IMP to the trial participants at the baseline visit; paracetamol was to be used as rescue medication if and as needed (up to 1000 mg per day); use of rescue medication was not allowed within 6 hours before attending the study clinic for the study visits. At each visit, the patient was expected to bring the box with rescue medication and a record was to be made of the use since the last visit (total number of tablets used; number of days with use of more than 2 tablets per day)

Evidence for comparator:

Vehicle control cutaneous solution indistinguishable from the investigational test drug Pennsaid 2% w/w cutaneous solution

Actual start date of recruitment	01 June 2015
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: 126
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	125
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

126 outpatients with acute uncomplicated Grade I-II ankle sprain were recruited from 7 German study sites from 05.Aug.2015 to 14.Dec.2015. Enrolled patients were assigned at random to parallel group treatment with either test (Pennsaid 2%) or control (Vehicle Control) medication

Pre-assignment

Screening details:

126 female and male outpatients with acute uncomplicated grade I-II ankle sprain of recent onset without confounding co-morbidity or co-medications were screened and enrolled. At the first visit, eligible patients were evaluated for baseline criteria, were then randomised, and self-applied the 1st dose under supervision by investigator

Period 1

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

Blinding implementation details:

The clinical trial was double-blind. Patients, Investigator staff, persons performing the assessments, monitors and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data kept strictly confidential, accessible only to authorized persons, (2) identity of the treatments was concealed by use of IMPs identical in packaging, labeling, schedule of administration, appearance, odor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pennsaid-2%

Arm description:

Pennsaid-2% w/w cutaneous solution (containing 2% w/w diclofenac sodium plus 45.5% w/w DMSO) for topical application; Nuvo Pharmaceuticals Inc.

Arm type	Experimental
Investigational medicinal product name	Pennsaid 2% w/w cutaneous solution
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use

Dosage and administration details:

Two 1-gram actuations one to each side of the injured ankle twice daily for seven days. The first dose was administered at the trial site immediately after randomisation under supervision and on instruction of the investigator; subsequent doses were self-administered by the patient while ambulatory. Treatment lasted until the morning of the last treatment day (day D08).

Arm title	Vehicle Control

Arm description:

Matched control cutaneous solution for topical application containing no diclofenac sodium, but 45.5% w/w DMSO; Nuvo Pharmaceuticals Inc.

Arm type	Placebo
Investigational medicinal product name	Vehicle Control
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use

Dosage and administration details:

Two 1-gram actuations one to each side of the injured ankle twice daily for seven days. The first dose was administered at the trial site immediately after randomisation under supervision and on instruction of the investigator; subsequent doses were self-administered by the patient while ambulatory. Treatment lasted until the morning of the last treatment day (day D08).

Number of subjects in period 1	Pennsaid-2%	Vehicle Control
Started	63	63
Completed	61	63
Not completed	2	0
Consent withdrawn by subject	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Pennsaid-2%
Reporting group description:	
Pennsaid-2% w/w cutaneous solution (containing 2% w/w diclofenac sodium plus 45.5% w/w DMSO) for topical application; Nuvo Pharmaceuticals Inc.	
Reporting group title	Vehicle Control
Reporting group description:	
Matched control cutaneous solution for topical application containing no diclofenac sodium, but 45.5% w/w DMSO; Nuvo Pharmaceuticals Inc.	

Reporting group values	Pennsaid-2%	Vehicle Control	Total
Number of subjects	63	63	126
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	62	63	125
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	34.57	33.33	
standard deviation	± 13.09	± 12.02	-
Gender categorical			
Units: Subjects			
Female	29	34	63
Male	34	29	63
POM (Pain on Movement)			
Pain intensity on controlled standardised movement of the injured ankle executed by the investigator and scored on a 100 mm visual analogue scale (VAS)			
Units: mm			
arithmetic mean	73.70	73.87	
standard deviation	± 12.32	± 11.14	-
PAR (Pain at Rest)			
After relaxing for about at least 10 minutes, the patient was asked to score his pain at rest in answer to the question: "How would you describe your ankle pain right now?" ("Wie würden Sie die Schmerzen in Ihrem Sprunggelenk in diesem Moment beschreiben?"). The answer was to be scored on a 100 mm VAS			
Units: mm			
arithmetic mean	30.32	33.37	
standard deviation	± 20.81	± 22.19	-
Ankle Swelling			
Ankle swelling was measured by the Figure-of-eight-method. Circumference was measured on both ankles. Swelling is calculated as the difference between the injured and the non-injured contralateral ankle			

Units: mm			
arithmetic mean	1.93	1.58	
standard deviation	± 1.14	± 1.11	-
Ankle Tenderness			
Tenderness was measured using a calibrated algometer on an area of 1 cm² at one of the four points of reference at the centre of the injured area that was first tested and confirmed to be the most sensitive on palpation; this selected point was then used throughout. The patient was instructed to indicate onset of pain with a verbal cue such as "Yes" or "Stop" or raising his/her hand. Effect-relevant tenderness was calculated as the difference in PPT (algometer pressure when the patient reports onset of pain) for the injured minus the non-injured foot			
Units: N/cm²			
arithmetic mean	36.40	31.97	
standard deviation	± 14.34	± 11.25	-
Ankle function (Karlsson Score)			
The patient scored (VRS) eight domains: pain, swelling, instability, stiffness, stair climbing, running, work activities, and the use of a support device. The maximum score equals 90. The patient scores his replies to the various questions on a printed questionnaire in national language made available to this purpose			
Units: sum of scores			
arithmetic mean	34.49	37.06	
standard deviation	± 12.57	± 15.50	-

End points

End points reporting groups

Reporting group title	Pennsaid-2%
Reporting group description:	
Pennsaid-2% w/w cutaneous solution (containing 2% w/w diclofenac sodium plus 45.5% w/w DMSO) for topical application; Nuvo Pharmaceuticals Inc.	
Reporting group title	Vehicle Control
Reporting group description:	
Matched control cutaneous solution for topical application containing no diclofenac sodium, but 45.5% w/w DMSO; Nuvo Pharmaceuticals Inc.	

Primary: POM (Pain on Movement) - D05

End point title	POM (Pain on Movement) - D05
End point description:	
End point type	Primary
End point timeframe:	
POM: D05 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-29.59 (-34.23 to -24.94)	-26.11 (-30.76 to -21.45)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description:	
Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.36
upper limit	2.39

Secondary: POM (Pain on Movement) - D03

End point title	POM (Pain on Movement) - D03

End point description:

End point type	Secondary

End point timeframe:

POM (Pain on Movement) - D03 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-17.17 (-20.36 to -13.98)	-11.96 (-15.15 to -8.76)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.25
upper limit	-1.17

Secondary: POM (Pain on Movement) - D08

End point title	POM (Pain on Movement) - D08

End point description:

End point type	Secondary

End point timeframe:

POM (Pain on Movement) - D08 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-46.53 (-52.09 to -40.97)	-42.52 (-48.08 to -36.95)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2603
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.05
upper limit	3.02

Secondary: PAR (Pain at Rest) - D03

End point title	PAR (Pain at Rest) - D03

End point description:

End point type	Secondary

End point timeframe:

PAR (Pain at Rest) - D03 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-6.25 (-8.63 to -3.86)	-5.10 (-7.65 to -2.56)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4283
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	1.7

Secondary: PAR (Pain at Rest) - D05

End point title	PAR (Pain at Rest) - D05

End point description:

End point type	Secondary

End point timeframe:

PAR (Pain at Rest) - D05 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-11.27 (-14.22 to -8.32)	-11.83 (-14.97 to -8.68)		

Statistical analyses

Statistical analysis title	between-treatemnt difference of change from D01

Statistical analysis description:

Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7549
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	4.08

Secondary: PAR (Pain at Rest) - D08

End point title	PAR (Pain at Rest) - D08

End point description:

End point type	Secondary

End point timeframe:

PAR (Pain at Rest) - D08 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: mm				
least squares mean (confidence interval 95%)	-17.44 (-20.36 to -14.52)	-18.56 (-21.67 to -15.44)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Mean changes from baseline were compared between treatment by analysis of covariance (ANCOVA) with treatment group and center as main effects and baseline as covariate. Treatment-by-center interaction was not part of the primary efficacy analysis model. LOCF was used for patients with premature study treatment discontinuation; LO before any non-allowed use of rescue treatment was carried forward for all patients with any non-allowed use of rescue medication

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.528
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.37
upper limit	4.6

Secondary: Tenderness - D03

End point title	Tenderness - D03

End point description:

End point type	Secondary

End point timeframe:

Tenderness - D03 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: n/cm2				
arithmetic mean (standard deviation)	-9.10 (± 11.06)	-4.52 (± 6.32)		

Statistical analyses

Statistical analysis title	Between treatment difference
Statistical analysis description: Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0055
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.77
upper limit	-1.4

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description: Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0055
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.77
upper limit	-1.4

Secondary: Tenderness - D05

End point title	Tenderness - D05

End point description:

End point type	Secondary
End point timeframe: Tenderness - D05 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: n/cm2				
arithmetic mean (standard deviation)	-15.49 (± 12.63)	-10.78 (± 8.18)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description: Students t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.47
upper limit	-0.95

Secondary: Tenderness - D08	
End point title	Tenderness - D08
End point description:	

End point type	Secondary
End point timeframe: Tenderness - D08 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: n/cm2				
arithmetic mean (standard deviation)	-24.23 (± 14.68)	-18.25 (± 10.41)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description: Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0104
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-5.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.49
upper limit	-1.47

Secondary: Ankle swelling - D03

End point title	Ankle swelling - D03
End point description:	
End point type	Secondary
End point timeframe: Ankle swelling - D03 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: mm				
arithmetic mean (standard deviation)	-0.69 (± 0.86)	-0.29 (± 0.51)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description:	
Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	-0.15

Secondary: Ankle Swelling - D05

End point title	Ankle Swelling - D05
End point description:	
End point type	Secondary
End point timeframe:	
Ankle Swelling - D05 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: mm				
arithmetic mean (standard deviation)	-1.05 (± 1.04)	-0.57 (± 0.59)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description:	
Student t-test	
Comparison groups	Vehicle Control v Pennsaid-2%

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.19

Secondary: Ankle Swelling - D08

End point title	Ankle Swelling - D08

End point description:

End point type	Secondary

End point timeframe:

Ankle Swelling - D08 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: mm				
arithmetic mean (standard deviation)	-1.44 (± 1.20)	-0.97 (± 0.89)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Student t-test

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0142
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.1

Secondary: Ankle joint function (Karlsson Score) - D03

End point title	Ankle joint function (Karlsson Score) - D03
End point description:	
End point type	Secondary
End point timeframe:	
Ankle joint function (Karlsson Score) - D03 change from D01	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: sum of scores				
arithmetic mean (standard deviation)	10.68 (± 10.19)	6.59 (± 7.35)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description:	
Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0115
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	4.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	7.23

Secondary: Ankle joint function (Karlsson Score) - D05

End point title	Ankle joint function (Karlsson Score) - D05

End point description:

End point type	Secondary

End point timeframe:

Ankle joint function (Karlsson Score) - D05 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: sum of scores				
arithmetic mean (standard deviation)	21.21 (± 12.86)	17.92 (± 12.83)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01

Statistical analysis description:

Student t-test

Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1549
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	3.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	7.84

Secondary: Ankle joint function (Karlsson Score) - D08

End point title	Ankle joint function (Karlsson Score) - D08

End point description:

End point type	Secondary

End point timeframe:

Ankle joint function (Karlsson Score) - D08 change from D01

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: sum of scores				
arithmetic mean (standard deviation)	35.52 (± 14.87)	29.03 (± 16.50)		

Statistical analyses

Statistical analysis title	Between-treatment difference of change from D01
Statistical analysis description: Student t-test	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	6.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	12.08

Secondary: PGAB (Patient General Assessment of Benefit)

End point title	PGAB (Patient General Assessment of Benefit)
End point description:	
End point type	Secondary
End point timeframe: End-of-treatment (D08)	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: number of subjects				
very good	21	6		
good	27	24		
fair	10	28		
poor	3	5		
very poor	0	0		

missing	2	0		

Statistical analyses

Statistical analysis title	PGAB - Between-treatment difference
Statistical analysis description: Cochran-Mantel-Haenzel test stratified by visit (D05, D08)	
Comparison groups	Pennsaid-2% v Vehicle Control
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: PGAS (Patient General Assessment of Satisfaction)

End point title	PGAS (Patient General Assessment of Satisfaction)
End point description:	
End point type	Secondary
End point timeframe: End-of-treatment (D08)	

End point values	Pennsaid-2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: number of subjects				
excellent	1	2		
very good	18	4		
good	26	22		
fair	13	28		
poor	3	7		
missing	2	0		

Statistical analyses

Statistical analysis title	Between-treatment difference
Statistical analysis description: Cochran-Mantel-Haenzel test stratified by visit (D05, D08)	
Comparison groups	Pennsaid-2% v Vehicle Control

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout study, from enrolment to end-of-trial on D08; in the event of unresolved safety findings at D08, post-D08 follow-up was provided

Adverse event reporting additional description:

Adverse events (AE) were defined as any untoward change in wellbeing on study. AE were either reported by the trial participants to the investigator or were observed findings by the investigator on visits D03, D05, or D08. The event was categorised as treatment-emergent if its onset was subsequent to administration of the first dose

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Pennsaid-2%

Reporting group description:

Treatment with Pennsaid 2% w/w cutaneous solution two 1-gram actuations, on to each side of the injured ankle twice daily for 7 days

Reporting group title	Vehicle Control

Reporting group description:

Treatment with Pennsaid matched vehicle control cutaneous solution two 1-gram actuations, on to each side of the injured ankle twice daily for 7 days

Serious adverse events	Pennsaid-2%	Vehicle Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Pennsaid-2%	Vehicle Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 63 (20.63%)	13 / 63 (20.63%)	
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Application site dryness			
subjects affected / exposed	5 / 63 (7.94%)	5 / 63 (7.94%)	
occurrences (all)	5	5	
Application site pruritus			
subjects affected / exposed	5 / 63 (7.94%)	5 / 63 (7.94%)	
occurrences (all)	5	5	
Application site paraesthesia			
subjects affected / exposed	3 / 63 (4.76%)	2 / 63 (3.17%)	
occurrences (all)	3	2	
Application site exfoliation			
subjects affected / exposed	2 / 63 (3.17%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Application site erythema			
subjects affected / exposed	0 / 63 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Product taste abnormal			
subjects affected / exposed	3 / 63 (4.76%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 63 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Infections and infestations			
Rash pustular			
subjects affected / exposed	1 / 63 (1.59%)	0 / 63 (0.00%)	
occurrences (all)	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

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

none

Notes: