Clinical trial results:
A multi-centre, randomised, controlled, double-blind, parallel-group study on the efficacy and safety of Pennsaid-2% topical skin solution in patients with Grade I-II ankle sprain

Summary

EudraCT number	2016-002620-92
Trial protocol	DE
Global end of trial date	30 March 2017

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-C-2016/P-3-02

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 Road, Unit 610, Mississauga, Canada, L5N 6J5
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	01 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
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	10 November 2016
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: 134
Worldwide total number of subjects	134
EEA total number of subjects	134

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	131
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

134 outpatients with acute uncomplicated Grade I-II ankle sprain were recruited from 10 German study sites from Nov.2016 to Mar.2017. Enrolled patients were assigned at random to parallel group treatment with either test (Pennsaid 2%) or control (Vehicle Control) medication.

Pre-assignment

Screening details:

134 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	Subject, Investigator, Monitor, Data analyst, 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	68	66
Completed	68	66

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	68	66	134
Age categorical			
Eligible: Male or female aged 18 – 75 years (inclusive)			
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)	67	64	131
From 65-84 years	1	2	3
85 years and over	0	0	0
Age continuous			
mean age by treatment group			
Units: years			
arithmetic mean	36.8	38.6	
standard deviation	± 14.0	± 13.6	-
Gender categorical			
number of males and females by treatment group			
Units: Subjects			
Female	28	30	58
Male	40	36	76
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	71.0	71.5	
standard deviation	± 10.1	± 9.3	-
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	33.0	30.6	
standard deviation	± 21.5	± 19.3	-

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	1.74	1.79	
standard deviation	± 1.08	± 0.98	-
Ankle Tenderness			
Tenderness was measured using a calibrated algometer on an area of 1 cm^2 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/cm^2			
arithmetic mean	-28.74	-28.37	
standard deviation	± 13.66	± 14.04	-
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	36.88	36.53	
standard deviation	± 12.43	± 11.36	-

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 (D03)

End point title	POM (D03)
End point description:	
End point type	Primary
End point timeframe:	
POM on D03	

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	54.95 (51.83 to 58.06)	56.37 (53.18 to 59.55)		

Statistical analyses

Statistical analysis title	Between-treatment difference
Statistical analysis description:	
Least square adjusted means of the POM on D03 by treatment; point estimate and SEM of the between-treatment difference and corresponding 95% CI as estimated by ANCOVA with the baseline POM as covariate and treatment and centre as factors [FAS]	
Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.504
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.61
upper limit	2.77

Secondary: POM - Time course (D03)

End point title	POM - Time course (D03)

End point description:

End point type	Secondary

End point timeframe:

Time course of POM over treatment - D03

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	54.69 (51.53 to 57.86)	56.13 (52.90 to 59.37)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the POM and change of POM from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline POM as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5074
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	2.85

Secondary: POM - Time course (D05)

End point title	POM - Time course (D05)

End point description:

End point type	Secondary

End point timeframe:

Time course of POM over treatment - D05

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	37.93 (33.99 to 41.86)	41.77 (37.76 to 45.78)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the POM and change of POM from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline POM as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1642
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.28
upper limit	1.59

Secondary: POM - Time course (D08)

End point title	POM - Time course (D08)

End point description:

End point type	Secondary

End point timeframe:

Time course of POM over treatment - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	19.99 (15.64 to 24.33)	27.98 (23.56 to 32.41)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the POM and change of POM from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline POM as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0099
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.03
upper limit	-1.96

Secondary: PAR - Time Course (D03)

End point title	PAR - Time Course (D03)

End point description:

End point type	Secondary

End point timeframe:

Time course of pain at rest (PAR) over treatment - D03

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	23.09 (20.52 to 25.66)	23.54 (20.95 to 26.12)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the PAR and change of PAR from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline PAR as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8026
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	3.09

Secondary: PAR - Time Course (D05)

End point title	PAR - Time Course (D05)

End point description:

End point type	Secondary

End point timeframe:

Time course of PAR over treatment - D05

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	14.41 (11.81 to 17.02)	16.23 (13.61 to 18.85)		

Statistical analyses

Statistical analysis title	Between treatment difference

Statistical analysis description:

Least square adjusted means of the PAR and change of PAR from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline PAR as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3171
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	1.77

Secondary: PAR - Time Course (D08)

End point title	PAR - Time Course (D08)

End point description:

End point type	Secondary

End point timeframe:

Time course of PAR over treatment - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	5.85 (3.28 to 8.43)	8.43 (5.84 to 11.02)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the PAR and change of PAR from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline PAR as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1512
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.11
upper limit	0.96

Secondary: Ankle Swelling - Time Course (D03)

End point title	Ankle Swelling - Time Course (D03)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Swelling over treatment - D03

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	1.51 (1.36 to 1.66)	1.34 (1.19 to 1.50)		

Statistical analyses

Statistical analysis title	Between-treatment Difference

Statistical analysis description:

Least square adjusted means of the Ankle Swelling and change of Ankle Swelling from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Swelling as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.38

Secondary: Ankle Swelling - Time Course (D05)

End point title	Ankle Swelling - Time Course (D05)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Swelling over treatment - D05

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	1.01 (0.87 to 1.15)	0.99 (0.84 to 1.13)		

Statistical analyses

Statistical analysis title	Between-treatment diference

Statistical analysis description:

Least square adjusted means of the Ankle Swelling and change of Ankle Swelling from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Swelling as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.22

Secondary: Ankle Swelling - Time Course (D08)

End point title	Ankle Swelling - Time Course (D08)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Swelling over treatment - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: mm				
least squares mean (confidence interval 95%)	0.46 (0.32 to 0.61)	0.63 (0.48 to 0.78)		

Statistical analyses

Statistical analysis title	Between-treatemnt difference

Statistical analysis description:

Least square adjusted means of the Ankle Swelling and change of Ankle Swelling from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Swelling as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1042
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.04

Secondary: Ankle Tenderness - Time Course (D03)

End point title	Ankle Tenderness - Time Course (D03)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Tenderness - D03

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: N/cm²				
least squares mean (confidence interval 95%)	-23.05 (-24.82 to -21.29)	-24.69 (-26.49 to -22.88)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the Ankle Tenderness and change of Ankle Tenderness from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Tenderness as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1776
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	4.02

Secondary: Ankle Tenderness - Time Course (D05)

End point title	Ankle Tenderness - Time Course (D05)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Tenderness (D05)

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: N/cm²				
least squares mean (confidence interval 95%)	-17.70 (-19.97 to -15.42)	-18.80 (-21.12 to -16.48)		

Statistical analyses

Statistical analysis title	Between-treatment difference
Statistical analysis description:	
Least square adjusted means of the Ankle Tenderness and change of Ankle Tenderness from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Tenderness as covariate, treatment, visit and treatment-by-visit as factors [FAS])	
Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.487
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	4.25

Secondary: Ankle Tenderness - Time Course (D08)

End point title	Ankle Tenderness - Time Course (D08)
End point description:	
End point type	Secondary
End point timeframe:	
Time course of Ankle Tenderness over treatment - D08	

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: N/cm²				
least squares mean (confidence interval 95%)	-12.60 (-15.09 to -10.11)	-12.82 (-15.35 to -10.28)		

Statistical analyses

Statistical analysis title	Between-treatemnt difference

Statistical analysis description:

Least square adjusted means of the Ankle Tenderness and change of Ankle Tenderness from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Tenderness as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9013
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	3.68

Secondary: Ankle Function | Karlsson Score - Time Course (D03)

End point title	Ankle Function | Karlsson Score - Time Course (D03)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Function (Karlsson Score) - D03

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: sum of scores				
least squares mean (confidence interval 95%)	47.03 (44.73 to 49.33)	43.73 (41.38 to 46.09)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the Ankle Function and change of Ankle Function from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Function as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0383
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	6.41

Secondary: Ankle Function | Karlsson Score - Time Course (D05)

End point title	Ankle Function | Karlsson Score - Time Course (D05)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Function (Karlsson Score) - D05

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: sum of scores				
least squares mean (confidence interval 95%)	58.41 (55.74 to 61.09)	53.34 (50.61 to 56.08)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the Ankle Function and change of Ankle Function from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Function as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	5.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	8.75

Secondary: Ankle Function | Karlsson Score - Time Course (D08)

End point title	Ankle Function | Karlsson Score - Time Course (D08)

End point description:

End point type	Secondary

End point timeframe:

Time course of Ankle Function (Karlsson Score) - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: sum of scores				
least squares mean (confidence interval 95%)	72.66 (69.53 to 75.80)	66.45 (63.25 to 69.65)		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Least square adjusted means of the Ankle Function and change of Ankle Function from D01 for the on-treatment visits D03 to D08 estimated by MMRM with the baseline Ankle Function as covariate, treatment, visit and treatment-by-visit as factors [FAS])

Comparison groups	Pennsaid 2% v Vehicle Control

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0055
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	10.57

Secondary: PGAB (Patient´s global assessment of benefit)

End point title	PGAB (Patient´s global assessment of benefit)

End point description:

End point type	Secondary

End point timeframe:

PGAB (Patient´s global assessment of benefit) - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: number of subjects				
No benefit	10	15		
Little benefit	23	31		
Much benefit	35	20		

Statistical analyses

Statistical analysis title	Between treatment comparison of number of subjects

Statistical analysis description:

Cochran-Mantel-Haenzel test of the between-treatment differences stratified by centre (Van Elteren test)

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0164
Method	Mantel-Haenszel

Secondary: PGAS (Patient Global Assessment Satisafaction)

End point title	PGAS (Patient Global Assessment Satisafaction)

End point description:

End point type	Secondary

End point timeframe:

PGAS (Patient Global Assessment Satisfaction) - D08

End point values	Pennsaid 2%	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: number of subjects				
very satisfied	33	22		
little satisfied	24	25		
little dissatisified	10	16		
very dissatisfied	1	3		

Statistical analyses

Statistical analysis title	Between-treatment difference

Statistical analysis description:

Cochran-Mantel-Haenzel test of the between-treatment differences stratified by centre (Van Elteren test)

Comparison groups	Pennsaid 2% v Vehicle Control
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0499
Method	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	19.1

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 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 / 68 (0.00%)	0 / 66 (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	6 / 68 (8.82%)	7 / 66 (10.61%)	
General disorders and administration site conditions			
Application site discomfort			
subjects affected / exposed	1 / 68 (1.47%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Application site dryness			

subjects affected / exposed	5 / 68 (7.35%)	3 / 66 (4.55%)	
occurrences (all)	5	3	
Application site erythema			
subjects affected / exposed	1 / 68 (1.47%)	3 / 66 (4.55%)	
occurrences (all)	1	4	
Application site exfoliation			
subjects affected / exposed	2 / 68 (2.94%)	1 / 66 (1.52%)	
occurrences (all)	2	1	
Application site irritation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Application site pruritus			
subjects affected / exposed	3 / 68 (4.41%)	4 / 66 (6.06%)	
occurrences (all)	3	4	
Psychiatric disorders			
Stress			
subjects affected / exposed	1 / 68 (1.47%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2017	16.Jan.2017 AM-01: regulating the effectively participating investigators and trial sites

Notes:

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: