Clinical trial results:
A single centre, randomised, single-blind, parallel group single dose study to compare the speed of onset of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel in the relief of pain from strains, sprains and sports injuries.

Summary

EudraCT number	2015-005240-33
Trial protocol	GB
Global end of trial date	15 June 2016

Results information

Result version number	v1 (current)
This version publication date	26 May 2017
First version publication date	26 May 2017
Summary attachment (see zip file)	Clinical study report (Mentholatum CSR.pdf)

Trial information

Trial identification

Sponsor protocol code	MENTH001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Ascension Trial: Short name

Notes:

Sponsors

Sponsor organisation name	The Mentholatum Company
Sponsor organisation address	1 Redwood Avenue,Peel Park Campus, East Kilbride, United Kingdom, G74 5PE
Public contact	Dr Gordon Crawford, CPS Research and Patients Direct, +44 0141 946 7888, gordon@cpsresearch.co.uk
Scientific contact	Dr Gordon Crawford, CPS Research and Patients Direct, +44 0141 946 7888, gordon@cpsresearch.co.uk

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	15 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2016
Global end of trial reached?	Yes
Global end of trial date	15 June 2016
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 determine the time to onset of significant pain relief in patients with soft tissue injuries of ibuprofen gel, ibuprofen gel with levomenthol, and diclofenac gel.

Protection of trial subjects:

This was a non-invasive trial measuring pain relief in marketed products. The marketed products used have a well established pain relief profile.

Background therapy: -

Evidence for comparator:

Deep Relief (contains ibuprofen and levomenthol) and an ibuprofen gel product were compared in this study in terms of speed of onset so that any differences could be attributed to the levomenthol in Deep Relief.

Voltarol Pain-eze Emugel was used to compare the speed of onset between diclofenac and ibuprofen.

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 182
Worldwide total number of subjects	182
EEA total number of subjects	182

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)	5
Adults (18-64 years)	176
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited into the study via referrals from local pharmacies, healthcare professionals, or by direct responses from study advertising. Those who referred to the study or responding to an advertisement spoke to a trained representative who asked them questions to determine whether they should be included in the trial.

Pre-assignment

Screening details:

A total of 762 repondents were screened by telephone. Patients admitted if they gave written informed consent, were between the ages of 16 and 75 (inclusive), had an acute soft tissue injury, and had at least moderate pain (greater than or equal to 6 on an NRS for pain) at baseline. Patients randomised to one of 3 treatment groups.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Randomised treatment was administered by 1 trained member of staff and another supervised the assessments. This enabled both patient and staff supervising the assessments to remain blinded. As levomenthol has a distinctive odour the assessment rooms were mentholised to mask this. Drug supplies were packaged and labelled to GMP standards according to a computer produced randomisation schedule.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibuprofen

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ibuprofen gel 5% W/W
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects received a single trial medication pack containing 35g of Ibuprofen gel 5% W/W for application to skin at baseline. A single application of gel was applied according to product instructions by a trained member of staff.

Arm title	Diclofenac

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Diclofenac gel
Investigational medicinal product code	
Other name	Voltarol Pain-ese Emulgel
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Patients received a single trial pack containing 30g of Diclofenac gel (Voltarol Pain-ese Emulgel 1.16%). A single application of gel was applied to the skin according to product instructions by a trained member of staff

Arm title	Deep Relief
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ibuprofen gel 5% W/W with Levomenthol 3% W/W
Investigational medicinal product code	
Other name	Deep Relief
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Patients received a single trial pack containing 30g of Ibuprofen gel 5% W/W with Levomenthol 3% W/W for application to the skin. A single application was made according to product instructions by a trained member of staff

Number of subjects in period 1	Ibuprofen	Diclofenac	Deep Relief
Started	61	61	60
Completed	61	61	59
Not completed	0	0	1
Data collection method failed during follow up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	182	182	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age distribtuion for the 182 participants eligible to take part in the study			
Units: years			
arithmetic mean	36.18		
full range (min-max)	17 to 67	-	
Gender categorical Units: Subjects			
Female	109	109	
Male	73	73	
Ethnicity			
Ethnicity for the 182 subjects eligible to take part in the study			
Units: Subjects			
Caucasian	171	171	
Asian	6	6	
Afro-Caribbean	0	0	
Other	5	5	
Child bearing			
Child bearing potential for the 73 females eligible for the study			
Units: Subjects			
Yes	64	64	
No	118	118	
Duration of injury (days)			
Self-reported duration of injury for the 182 patients eligible to take part in the study			
Units: Subjects			
<1	0	0	
1 - 3	18	18	
4 - 7	27	27	
>7	137	137	

Site of injury			
Location of injury reported by the 182 patients eligible to take part in the study			
Units: Subjects			
Neck	14	14	
Shoulder	29	29	
Upper Limb	15	15	
Back	45	45	
Torso	0	0	
Lower Limb	79	79	
Type of injury			
Type of injury sustained by the 182 participants eligible for the study			
Units: Subjects			
Sprain/strain	129	129	
Muscular ache	42	42	
Bruise/soft tissue	11	11	
Sporting injury			
Details on whether or not the injury sustained by the 182 patients eligible for the study was a sporting injury			
Units: Subjects			
Yes	104	104	
No	78	78	
Baseline NRS pain score			
Pain scores at baseline for the 182 patients eligible to take part in the study			
Units: Subjects			
Six	41	41	
Seven	76	76	
Eight	51	51	
Nine	11	11	
Ten	3	3	

Subject analysis sets

Subject analysis set title	Females
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Female participants in the study.

Reporting group values	Females		
Number of subjects	73		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous			
Age distribtuion for the 182 participants eligible to take part in the study			
Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
Ethnicity			
Ethnicity for the 182 subjects eligible to take part in the study			
Units: Subjects			
Caucasian Asian Afro-Caribbean Other			
Child bearing			
Child bearing potential for the 73 females eligible for the study			
Units: Subjects			
Yes No	64 9		
Duration of injury (days)			
Self-reported duration of injury for the 182 patients eligible to take part in the study			
Units: Subjects			
<1 1 - 3 4 - 7 >7			
Site of injury			
Location of injury reported by the 182 patients eligible to take part in the study			
Units: Subjects			
Neck Shoulder Upper Limb Back Torso Lower Limb			
Type of injury			
Type of injury sustained by the 182 participants eligible for the study			
Units: Subjects			
Sprain/strain Muscular ache Bruise/soft tissue			
Sporting injury			
Details on whether or not the injury sustained by the 182 patients eligible for the study was a sporting injury			
Units: Subjects			
Yes No			
Baseline NRS pain score			
Pain scores at baseline for the 182 patients eligible to take part in the study			
Units: Subjects			

Six			
Seven			
Eight			
Nine			
Ten			

End points

End points reporting groups

Reporting group title	Ibuprofen
Reporting group description: -	
Reporting group title	Diclofenac
Reporting group description: -	
Reporting group title	Deep Relief
Reporting group description: -	
Subject analysis set title	Females
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Female participants in the study.	

Primary: time to onset of significant pain relief

End point title	time to onset of significant pain relief
End point description:	
Time to onset of significant pain relief recorded at defined intervals from gel application (t=0 min) and end of study (t=120 min) Significant pain relief defined as a 2-point drop in pain score from baseline (measured by an 11-point ordinal NRS pain scale)	
End point type	Primary
End point timeframe:	
Time to onset of significant pain relief difference from 0 to 2 hrs	

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: minute				
median (standard error)	25 (± 4.875)	20 (± 3.219)	20 (± 3.189)	

Statistical analyses

Statistical analysis title	Equality of survival distributions (120min)
Statistical analysis description:	
Survival analysis used to test for equality of survival distributions at 120 min	
Comparison groups	Diclofenac v Ibuprofen v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.313 [1]
Method	Logrank

Notes:

[1] - P-value was greater than the 5% significance level. Therefore, there was no evidence of a difference between the three treatment groups at 120 min

Statistical analysis title	Equality of survival distribution (30min)

Statistical analysis description:

Survival analysis to examine the equality of the survival times for the three treatments at 30 minutes

Comparison groups	Diclofenac v Deep Relief v Ibuprofen
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.238 [2]
Method	Logrank

Notes:

[2] - The p-value was greater than the 5% significance level. Therefore, there was no evidence of a difference between the three treatment groups at 30 minutes

Secondary: Change in pain scores

End point title	Change in pain scores

End point description:

End point type	Secondary

End point timeframe:

Change in the median pain score between baseline and 2 hours

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
number (not applicable)	-2	-3	-3	

Statistical analyses

Statistical analysis title	Median change in pain scores
Comparison groups	Ibuprofen v Diclofenac v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.087 [3]
Method	Kruskal-wallis

Notes:

[3] - The p-value is greater than the 5% significance level and so there is no evidence of a difference between the three groups

Secondary: Warming sensations within the first five minutes

End point title	Warming sensations within the first five minutes

End point description:

End point type	Secondary

End point timeframe:

Number of patients experiencing warming sensations within the first five minutes

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
Reported cooling	5	12	16	

Statistical analyses

Statistical analysis title	Analysis of warming
Comparison groups	Ibuprofen v Diclofenac v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026 [4]
Method	Chi-squared

Notes:

[4] - P-value less than the 5% significance level. There was evidence to suggest an association between treatment group and reported warming within the first 5 minutes

Secondary: Cooling sensations within five minutes

End point title	Cooling sensations within five minutes

End point description:

End point type	Secondary

End point timeframe:

Number of patients reporting cooling sensations within the first 5 minutes

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number	49	46	48	

Statistical analyses

Statistical analysis title	Cooling sensations
Comparison groups	Ibuprofen v Diclofenac v Deep Relief

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.692 [5]
Method	Chi-squared

Notes:

[5] - Since the p-value is greater than 0.05, there is no evidence of an association between treatment group and cooling within the first five minutes

Secondary: Functional impairment at 2 hours

End point title	Functional impairment at 2 hours

End point description:

End point type	Secondary

End point timeframe:

Changes in functional impairment between baseline and 2 hours

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
number (not applicable)	-2	-2	-2	

Statistical analyses

Statistical analysis title	Analysis of changes to functional impairment
Comparison groups	Ibuprofen v Diclofenac v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.889 [6]
Method	Kruskal-wallis

Notes:

[6] - At the 5% significance level there was no evidence of a difference in the change in functional impairment scores among the three treatment groups between baseline and 2 hours

Secondary: Assessment of general/global pain relief at 2 hours

End point title	Assessment of general/global pain relief at 2 hours

End point description:

End point type	Secondary

End point timeframe:

Between baseline and 2 hours

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
median (full range (min-max))	5 (1 to 7)	4 (1 to 7)	4 (1 to 6)	

Statistical analyses

Statistical analysis title	Global pain relief

Statistical analysis description:

Global pain relief was coded to a 7 - point scale and the median values compared between the three groups. Levels: No relief, slight relief, mild relief, moderate relief, considerable relief, almost complete relief and complete relief

Comparison groups	Ibuprofen v Diclofenac v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [7]
Method	Kruskal-wallis

Notes:

[7] - P-value was less than 5% significance level so there was evidence to suggest that the general pain relief reported at 2 hours differed between the three treatment groups

Post-hoc: Proportions achieving significant pain relief

End point title	Proportions achieving significant pain relief

End point description:

End point type	Post-hoc

End point timeframe:

Differences between the proportion of people achieving significant pain relief at 30 minutes

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
number (not applicable)	0.557337	0.655738	0.711864	

Statistical analyses

Statistical analysis title	Test for two proportions
Comparison groups	Ibuprofen v Deep Relief

Number of subjects included in analysis	120
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.075 [8]
Method	t-test, 2-sided

Notes:

[8] - P-value was greater than the 5% significance level. There was no evidence to suggest that the proportion on Ibuprofen who achieved significant pain relief was different to the proportion on Deep Relief who achieved significant pain relief

Statistical analysis title	Diclofenac vs Deep Relief
Comparison groups	Diclofenac v Deep Relief
Number of subjects included in analysis	120
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.508 [9]
Method	t-test, 2-sided

Notes:

[9] - P-value is greater than 5% significance level. There is no evidence to suggest that the proportion on Deep relief who achieved significant pain relief was different to the proportion on Diclofenac who achieved significant pain relief

Post-hoc: Number of patients achieving significant pain relief

End point title	Number of patients achieving significant pain relief

End point description:

End point type	Post-hoc

End point timeframe:

Number of people achieving significant pain relief at time points 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
1.0	1	4	1	
2.5	5	6	3	
5.0	6	10	9	
7.5	12	13	15	
10	17	20	23	
12.5	20	26	26	
15	22	30	29	
20	29	35	32	
25	32	39	41	
30	34	40	42	
40	40	44	45	
50	43	47	48	
60	44	48	48	
75	46	48	50	
90	47	48	51	

105	48	49	52	
120	50	50	53	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number reporting cooling at 2 hours

End point title	Number reporting cooling at 2 hours

End point description:

End point type	Post-hoc

End point timeframe:

2 hours (120 minutes)

End point values	Ibuprofen	Diclofenac	Deep Relief	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	61	59	
Units: number				
Yes	9	10	27	

Statistical analyses

Statistical analysis title	Difference between number reporting cooling at 2 h
Comparison groups	Ibuprofen v Diclofenac v Deep Relief
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.001 [10]
Method	Chi-squared

Notes:

[10] - The p-value is less than 5% significance level so there is evidence to suggest significantly more people in the deep relief group reported cooling (46%) than in the other groups (16% and 15%)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were asked if they had any untoward signs or symptoms (not including symptoms of their injury) at the pre-dose time-point, at the end of the two hour assessment period and at the follow up (up to 72 hours after leaving the assessment centre).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Diclofenac group

Reporting group description:

Subjects who were treated with diclofenac gel.

Reporting group title	Ibuprofen

Reporting group description:

subjects who were exposed to ibuprofen gel

Reporting group title	Deep Relief

Reporting group description:

Subjects who were exposed to Deep Relief gel.

Serious adverse events	Diclofenac group	Ibuprofen	Deep Relief
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Fracture treatment	Additional description: The event was unrelated to the study medication-diclofenac group.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Diclofenac group	Ibuprofen	Deep Relief
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 61 (4.92%)	1 / 61 (1.64%)	1 / 59 (1.69%)
Nervous system disorders			

Head discomfort	Additional description: Pressure on forehead. Considered not related to study medication.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Feeling hot	Additional description: Warming sensation on the neck. Considered unlikely to be related to the study medication.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Application site reaction	Additional description: Red itchy skin where gel applied. Mild severity. Considered related to study medication.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling	Additional description: Swelling to feet and ankles. Mild severity. Considered not related to study medication.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 59 (1.69%)
occurrences (all)	0	0	1
Pyrexia	Additional description: Feeling high temperature. Mild severity. Considered not related to study medication.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Night sweats	Additional description: Considered not related to study medication		
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort	Additional description: Pressure at the base of back. Considered not related to study medication.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	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: