



Clinical trial results:

A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain

Summary

EudraCT number	2015-000404-25
Trial protocol	DE
Global end of trial date	21 July 2017

Results information

Result version number	v1 (current)
This version publication date	04 August 2018
First version publication date	04 August 2018

Trial information

Trial identification

Sponsor protocol code	1358.1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02700815
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.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	19 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 July 2017
Global end of trial reached?	Yes
Global end of trial date	21 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective was to compare the efficacy of a combination of topical diclofenac (2%) + capsaicin (0.075%) (diclofenac + capsaicin) versus placebo, diclofenac alone (2%), and capsaicin alone (0.075%) in the treatment of acute back or neck pain, and to assess the safety and tolerability of the combination of diclofenac and capsaicin in comparison to gels with diclofenac alone or capsaicin alone.

Protection of trial subjects:

All patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. The patients were informed that their personal trial related data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the patients. The patients were also informed that their medical records could be examined by Clinical Quality Assurance auditors appointed by BI, by members of the appropriate IEC/IRB, and by inspectors from regulatory authorities. Confidentiality of patient data was ensured by the use of depersonalised patient identification codes (patient numbers). The terms and conditions of the insurance cover were available to the investigator and the patients in the Investigator Site File (ISF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 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: 693
Country: Number of subjects enrolled	Russian Federation: 64
Worldwide total number of subjects	757
EEA total number of subjects	693

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	664
From 65 to 84 years	90
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo- and active treatment-controlled, double-blind, parallel-group study. Out of 757 enrolled patients with acute back or neck pain, 746 were randomised and treated with 4 topical treatments administered twice daily for 4 to 7 days.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that all subjects met all inclusion/exclusion criteria. Subjects were not to be entered to trial if any of the specific entry criteria were not met.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Gel

Arm description:

Patients were topically applied matching Placebo 2 gram (g) gel, twice daily with 12 ± 4 hours (h) between applications.

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

Dosage and administration details:

Topical application of matching Placebo 2 gram (g) gel, twice daily with 12 ± 4 hours (h) between applications.

Arm title	Capsaicin (0.075%) Gel
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Arm description:

Patients were topically applied Capsaicin 2 g gel (1.5 milligram (mg) Capsaicin), twice daily with 12 ± 4 hours (h) between applications.

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

Dosage and administration details:

Topically application of Capsaicin 2 g gel (1.5 milligram (mg) Capsaicin), twice daily with 12 ± 4 hours (h) between applications.

Arm title	Diclofenac (2%) Gel
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Arm description:

Patients were topically applied Diclofenac 2 g gel (40 milligram (mg) Diclofenac), twice daily with 12 ± 4 hours (h) between applications.

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

Dosage and administration details:

Topically application of Diclofenac 2 g gel (40 milligram (mg) Diclofenac), twice daily with 12 ± 4 hours (h) between applications.

Arm title	Diclofenac (2%) +Capsaicin (0.075%) Gel
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Arm description:

Patients were topically applied Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.

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

Dosage and administration details:

Topical application of Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.

Investigational medicinal product name	Capsaicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Topical application of Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.

Number of subjects in period 1^[1]	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel
Started	75	223	223
Completed	74	216	219
Not completed	1	7	4
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	6	2
Refusal to continue medication	-	1	-
Lost to follow-up	1	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1^[1]	Diclofenac (2%) +Capsaicin (0.075%) Gel
Started	225
Completed	218
Not completed	7
Consent withdrawn by subject	-

Adverse event, non-fatal	3
Refusal to continue medication	1
Lost to follow-up	1
Lack of efficacy	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Placebo Gel
Reporting group description: Patients were topically applied matching Placebo 2 gram (g) gel, twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Capsaicin (0.075%) Gel
Reporting group description: Patients were topically applied Capsaicin 2 g gel (1.5 milligram (mg) Capsaicin), twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Diclofenac (2%) Gel
Reporting group description: Patients were topically applied Diclofenac 2 g gel (40 milligram (mg) Diclofenac), twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Diclofenac (2%) +Capsaicin (0.075%) Gel
Reporting group description: Patients were topically applied Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.	

Reporting group values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel
Number of subjects	75	223	223
Age categorical			
Units: Subjects			

Age Continuous			
Age of all patients included in the trial. Treated Set (TS): All randomised patients who used at least 1 dose of study medication were included in the TS. Patients who received the wrong treatment were analysed within the planned (randomised) treatment group in the efficacy analysis and within the actual treatment group in the safety analysis (TS, as treated).			
Units: years			
arithmetic mean	45.3	43.2	44.0
standard deviation	± 14.78	± 15.42	± 15.96
Sex: Female, Male			
Gender distribution of all patients included in the trial. TS was used to assess gender of all patients.			
Units: Subjects			
Female	44	128	136
Male	31	95	87
Race (NIH/OMB)			
Race of all patients included in the trial. TS was used to assess race of all patients.			
Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	2	3	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	73	216	218
More than one race	0	2	4
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Ethnicity of all patients included in the trial. TS was used to assess ethnicity of all patients.			

Units: Subjects			
Hispanic or Latino	0	3	3
Not Hispanic or Latino	75	220	220
Unknown or Not Reported	0	0	0
Country			
The list of countries from which the respective number of patients had been enrolled. TS was used to assess country of participation of all patients.			
Units: Subjects			
Germany	69	205	205
Russia	6	18	18
Application site			
Pain on Movement (POM) was assessed by patients on performance of standardized, muscle group specific movements measured using a VAS on application sites. Back and Neck were defined as application sites for this study. Acute back and neck pain was studied in this trial. Number of patients with either neck or back as an application site were presented here. TS was used to assess application site of all patients.			
Units: Subjects			
Neck	45	126	129
Back	30	97	94
Pain on movement of worst procedure (POMwp)			
POM was used to assess pain measurement for back and neck. The standard movements have been established for which the measurement was taken. POMwp was the POM measure that gave the highest score at baseline; i.e. POM of worst procedure. Pain intensity was assessed at rest after standing in an upright position relatively motionless for 1 minute. The pain was evaluated by asking patient 'How would you rate your pain right now?' and by using a visual analogue scale (VAS) ranging from 0-10 cm wherein 0 cm = no pain to 10 cm = worst pain possible. TS was used to assess POMwp of all patients.			
Units: Unit on scale from 0 to 10			
arithmetic mean	7.20	7.22	7.29
standard deviation	± 1.246	± 1.157	± 1.274

Reporting group values	Diclofenac (2%) +Capsaicin (0.075%) Gel	Total	
Number of subjects	225	746	
Age categorical			
Units: Subjects			

Age Continuous			
Age of all patients included in the trial. Treated Set (TS): All randomised patients who used at least 1 dose of study medication were included in the TS. Patients who received the wrong treatment were analysed within the planned (randomised) treatment group in the efficacy analysis and within the actual treatment group in the safety analysis (TS, as treated).			
Units: years			
arithmetic mean	44.2		
standard deviation	± 15.49	-	
Sex: Female, Male			
Gender distribution of all patients included in the trial. TS was used to assess gender of all patients.			
Units: Subjects			
Female	136	444	
Male	89	302	
Race (NIH/OMB)			
Race of all patients included in the trial. TS was used to assess race of all patients.			
Units: Subjects			
American Indian or Alaska Native	1	2	
Asian	2	7	

Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	5	
White	216	723	
More than one race	3	9	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Ethnicity of all patients included in the trial. TS was used to assess ethnicity of all patients.			
Units: Subjects			
Hispanic or Latino	3	9	
Not Hispanic or Latino	222	737	
Unknown or Not Reported	0	0	
Country			
The list of countries from which the respective number of patients had been enrolled. TS was used to assess country of participation of all patients.			
Units: Subjects			
Germany	205	684	
Russia	20	62	
Application site			
Pain on Movement (POM) was assessed by patients on performance of standardized, muscle group specific movements measured using a VAS on application sites. Back and Neck were defined as application sites for this study. Acute back and neck pain was studied in this trial. Number of patients with either neck or back as an application site were presented here. TS was used to assess application site of all patients.			
Units: Subjects			
Neck	130	430	
Back	95	316	
Pain on movement of worst procedure (POMwp)			
POM was used to assess pain measurement for back and neck. The standard movements have been established for which the measurement was taken. POMwp was the POM measure that gave the highest score at baseline; i.e. POM of worst procedure. Pain intensity was assessed at rest after standing in an upright position relatively motionless for 1 minute. The pain was evaluated by asking patient 'How would you rate your pain right now?' and by using a visual analogue scale (VAS) ranging from 0-10 cm wherein 0 cm = no pain to 10 cm = worst pain possible. TS was used to assess POMwp of all patients.			
Units: Unit on scale from 0 to 10			
arithmetic mean	7.28		
standard deviation	± 1.148	-	

End points

End points reporting groups

Reporting group title	Placebo Gel
Reporting group description: Patients were topically applied matching Placebo 2 gram (g) gel, twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Capsaicin (0.075%) Gel
Reporting group description: Patients were topically applied Capsaicin 2 g gel (1.5 milligram (mg) Capsaicin), twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Diclofenac (2%) Gel
Reporting group description: Patients were topically applied Diclofenac 2 g gel (40 milligram (mg) Diclofenac), twice daily with 12 ± 4 hours (h) between applications.	
Reporting group title	Diclofenac (2%) +Capsaicin (0.075%) Gel
Reporting group description: Patients were topically applied Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.	

Primary: Change in POM between baseline and Day 2 evening, 1 hour after drug application

End point title	Change in POM between baseline and Day 2 evening, 1 hour after drug application
End point description: POM was used to assess pain measurement for back and neck. The standardized movements have been established for which the measurement was taken. POMwp was the POM measure that gave highest score at baseline i.e. POM of worst procedure. Pain intensity was assessed at rest after standing in an upright position motionless for 1 min. The pain was evaluated by asking patient How would you rate your pain right now? and by using a visual analogue scale (VAS) ranging from 0-10 cm wherein 0 cm = no pain to 10 cm = worst pain possible. Results presented here are adjusted mean change from baseline and standard error for POMwp in centimeters (cm). Full analysis set (FAS): All patients in treated set with a baseline value pre application for POMwp at Visit 1 and at least 1 POMwp value during assessment times at Visit 1 (Day 1 morning 1h after application), Visit 2 (Day 2, morning 1h after application), Visit 3 (Day 2 evening before application) or Visit 3 (Day 2 evening 1h after application)	
End point type	Primary
End point timeframe: Baseline and Day 2	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[1]	222 ^[2]	222 ^[3]	225 ^[4]
Units: Centimeter (cm)				
least squares mean (standard error)	-2.45 (± 0.252)	-3.26 (± 0.160)	-2.33 (± 0.160)	-3.05 (± 0.159)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between placebo and combination therapy diclofenac + capsaicin.

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0303
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.277

Notes:

[5] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between capsaicin and combination therapy diclofenac + capsaicin.

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.2886
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.197

Notes:

[6] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
Statistical analysis description: A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between diclofenac and combination therapy diclofenac + capsaicin.	
Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.33
Variability estimate	Standard error of the mean
Dispersion value	0.197

Notes:

[7] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Secondary: POMwp area under the curve (AUC) calculated from 0 to 72 hours (h) (POMwp AUC(0-72 h))

End point title	POMwp area under the curve (AUC) calculated from 0 to 72 hours (h) (POMwp AUC(0-72 h))
End point description: This is a key secondary endpoint. AUC for POMwp calculated from 0 to 72 h that is for first three treatment days using the trapezoidal rule divided by the observation time. The results presented here are adjusted mean and standard error for POMwp AUC (0-72 h) in centimeters (cm). TS was used to assess POMwp AUC.	
End point type	Secondary
End point timeframe: First 3 treatment days	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[8]	223 ^[9]	223 ^[10]	225 ^[11]
Units: cm				
least squares mean (standard error)	4.62 (± 0.213)	3.95 (± 0.145)	4.81 (± 0.145)	4.25 (± 0.143)

Notes:

[8] - TS

[9] - TS

[10] - TS

[11] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-72 h) between placebo and combination therapy diclofenac + capsaicin

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.0956
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.221

Notes:

[12] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-72 h) between capsaicin and combination therapy diclofenac + capsaicin

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.0564
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.157

Notes:

[13] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-72 h) between diclofenac and combination therapy diclofenac + capsaicin	
Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.157

Notes:

[14] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Secondary: POMwp Area under the curve (AUC) calculated from 0 to 120 hours (h) (POMwp AUC(0-120 h))

End point title	POMwp Area under the curve (AUC) calculated from 0 to 120 hours (h) (POMwp AUC(0-120 h))
End point description:	
This is a key secondary endpoint. AUC for POMwp calculated from 0 to 120 h that is for first five treatment days using the trapezoidal rule divided by the observation time. The results presented here are adjusted mean and standard error for POMwp AUC (0-120 h) in centimeters (cm). TS was used to assess POMwp AUC.	
End point type	Secondary
End point timeframe:	
First 5 treatment days	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[15]	223 ^[16]	223 ^[17]	225 ^[18]
Units: cm				
least squares mean (standard error)	3.92 (± 0.230)	3.10 (± 0.156)	4.10 (± 0.156)	3.41 (± 0.154)

Notes:

[15] - TS

[16] - TS

[17] - TS

[18] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-120 h) between placebo and combination therapy diclofenac + capsaicin

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0347
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.238

Notes:

[19] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-120 h) between capsaicin and combination therapy diclofenac + capsaicin

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.0622
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.169

Notes:

[20] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
An analysis of covariance (ANCOVA) was used to compare POMwp AUC(0-120 h) between diclofenac and combination therapy diclofenac + capsaicin	
Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	0.169

Notes:

[21] - ANCOVA includes treatment, country, and application site (back/neck) as fixed effects, and baseline POMwp as a continuous covariate. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Secondary: Number of patients with decrease in POMwp of at least 30% from baseline

End point title	Number of patients with decrease in POMwp of at least 30% from baseline
End point description:	
This outcome measures the pattern of number of patients with a decrease in POMwp of at least 30% from baseline at 1 hour after dosing on Day 2 evening. TS was used to assess decrease in POMwp.	
End point type	Secondary
End point timeframe:	
Baseline and day 2	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[22]	223 ^[23]	223 ^[24]	225 ^[25]
Units: Participants	34	150	107	134

Notes:

[22] - TS

[23] - TS

[24] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
A logistic regression was used to compare change in number of patients with a decrease in POMwp of at least 30% from baseline between placebo and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.	
Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.0202
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.21

Notes:

[26] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
A logistic regression was used to compare change in number of patients with a decrease in POMwp of at least 30% from baseline between capsaicin and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.	
Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.1206
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.732
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.09

Notes:

[27] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Statistical analysis title	Statistical analysis 3
Statistical analysis description: A logistic regression was used to compare change in number of patients with a decrease in POMwp of at least 30% from baseline between diclofenac and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.	
Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.0122
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.629
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	2.39

Notes:

[28] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Secondary: Number of patients with decrease in POMwp of at least 50% from baseline

End point title	Number of patients with decrease in POMwp of at least 50% from baseline
End point description: This outcome measures the pattern of number of patients with a decrease in POMwp of at least 50% from baseline at 1 hour after dosing on Day 2 evening. TS was used to assess decrease in POMwp.	
End point type	Secondary
End point timeframe: Baseline and day 2	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[29]	223 ^[30]	223 ^[31]	225 ^[32]
Units: Participants	20	95	50	85

Notes:

[29] - TS

[30] - TS

[31] - TS

[32] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

A logistic regression was used to compare change in number of patients with a decrease in POMwp of at

least 50% from baseline between placebo and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.0643
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.729
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	3.09

Notes:

[33] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
A logistic regression was used to compare change in number of patients with a decrease in POMwp of at least 50% from baseline between capsaicin and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.	
Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.3479
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.833
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.22

Notes:

[34] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
A logistic regression was used to compare change in number of patients with a decrease in POMwp of at least 50% from baseline between diclofenac and combination therapy diclofenac + capsaicin. The likelihood-ratio test was used to test for differences between treatments.	
Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.0004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3.22

Notes:

[35] - Logistic regression model include country and application site as covariates. Odds ratio was calculated as combination treatment/individual treatment.

Secondary: Change from baseline in POMwp (cm) at Day 6 morning

End point title	Change from baseline in POMwp (cm) at Day 6 morning
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End point description:

Pain on movement (POM) was used to assess pain measurement for back and neck pain. The standardized movements have been established for which the measurement was taken. POMwp was the POM measure that gave the highest score at baseline; i.e. POM of worst procedure. Pain intensity was assessed at rest after standing in an upright position relatively motionless for 1 minute. The pain was evaluated by asking patient 'How would you rate your pain right now?' and by using a visual analogue scale (VAS) ranging from 0-10 cm wherein 0 cm = no pain to 10 cm = worst pain possible. The results presented here are adjusted mean change from baseline and standard error for POMwp in centimeters (cm). TS was used to assess change from baseline in POMwp.

End point type	Secondary
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End point timeframe:

Baseline and Day 6

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[36]	223 ^[37]	223 ^[38]	225 ^[39]
Units: cm				
least squares mean (standard error)	-3.83 (± 0.282)	-5.08 (± 0.175)	-3.77 (± 0.175)	-4.88 (± 0.174)

Notes:

[36] - TS

[37] - TS

[38] - TS

[39] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between placebo and combination therapy diclofenac + capsaicin.

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
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Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[40]
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	-0.44
Variability estimate	Standard error of the mean
Dispersion value	0.313

Notes:

[40] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between capsaicin and combination therapy diclofenac + capsaicin.

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	= 0.3726
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.223

Notes:

[41] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in POMwp from baseline between diclofenac and combination therapy diclofenac + capsaicin.

Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
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Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	-0.68
Variability estimate	Standard error of the mean
Dispersion value	0.223

Notes:

[42] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline POMwp and baseline POMwp by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Secondary: Change from baseline in pressure algometry (PA) at day 2 evening before drug application

End point title	Change from baseline in pressure algometry (PA) at day 2 evening before drug application
End point description:	
PA is a method described to determine pressure pain threshold (PPT) by applying controlled pressure to a given body point. The results presented here are adjusted mean change from baseline and standard error for PA. TS was used to assess change from baseline in PA.	
End point type	Secondary
End point timeframe:	
Baseline and Day 2	

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[43]	223 ^[44]	223 ^[45]	225 ^[46]
Units: Newton/centimeter square (N/cm ²)				
least squares mean (standard error)	3.89 (± 0.795)	3.46 (± 0.526)	3.00 (± 0.530)	3.77 (± 0.526)

Notes:

[43] - TS

[44] - TS

[45] - TS

[46] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between placebo and combination therapy diclofenac + capsaicin.	
Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[47]
P-value	= 0.881
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	1.53
Variability estimate	Standard error of the mean
Dispersion value	0.844

Notes:

[47] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between capsaicin and combination therapy diclofenac + capsaicin.

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	= 0.6094
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	1.49
Variability estimate	Standard error of the mean
Dispersion value	0.601

Notes:

[48] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between diclofenac and combination therapy diclofenac + capsaicin.

Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
-------------------	---

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[49]
P-value	= 0.2047
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	1.95
Variability estimate	Standard error of the mean
Dispersion value	0.602

Notes:

[49] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Secondary: Change from baseline in pressure algometry (PA) at day 6 morning

End point title	Change from baseline in pressure algometry (PA) at day 6 morning
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End point description:

PA is a method described to determine pressure pain threshold (PPT) by applying controlled pressure to a given body point. The results presented here are adjusted mean change from baseline and standard error for PA. TS was used to assess change from baseline in PA.

End point type	Secondary
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End point timeframe:

Baseline and Day 6

End point values	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel	Diclofenac (2%) +Capsaicin (0.075%) Gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75 ^[50]	223 ^[51]	223 ^[52]	225 ^[53]
Units: Newton/centimeter square (N/cm ²)				
least squares mean (standard error)	8.01 (± 1.199)	9.38 (± 0.737)	7.64 (± 0.740)	9.66 (± 0.737)

Notes:

[50] - TS

[51] - TS

[52] - TS

[53] - TS

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between placebo and combination therapy diclofenac + capsaicin.

Comparison groups	Placebo Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
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Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority ^[54]
P-value	= 0.2193
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	4.27
Variability estimate	Standard error of the mean
Dispersion value	1.339

Notes:

[54] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between capsaicin and combination therapy diclofenac + capsaicin.

Comparison groups	Capsaicin (0.075%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	= 0.7672
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	2.15
Variability estimate	Standard error of the mean
Dispersion value	0.949

Notes:

[55] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Statistical analysis title	Statistical analysis 3
-----------------------------------	------------------------

Statistical analysis description:

A Mixed Model Repeat Measures (MMRM) analysis was used to compare change in PA from baseline between diclofenac and combination therapy diclofenac + capsaicin.

Comparison groups	Diclofenac (2%) Gel v Diclofenac (2%) +Capsaicin (0.075%) Gel
-------------------	---

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority ^[56]
P-value	= 0.0339
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	3.88
Variability estimate	Standard error of the mean
Dispersion value	0.95

Notes:

[56] - MMRM model included fixed effects of treatment, country, application site (back/neck), time and fixed covariates of baseline PA and baseline PA by time interaction. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 2 days after the last drug administration, i.e. up to 8 days.

Adverse event reporting additional description:

An adverse event (AE) was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event did not necessarily have to have a causal relationship with this treatment. TS (as treated) has been used for assessment of AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo Gel
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Reporting group description:

Patients were topically applied with matching Placebo 2 gram (g) gel, twice daily with 12 ± 4 hours (h) between applications.

Reporting group title	Capsaicin (0.075%) Gel
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Reporting group description:

Patients were topically applied with Capsaicin 2 g gel (1.5 milligram (mg) Capsaicin), twice daily with 12 ± 4 hours (h) between applications.

Reporting group title	Diclofenac (2%) Gel
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Reporting group description:

Patients were topically applied with Diclofenac 2 g gel (40 milligram (mg) Diclofenac), twice daily with 12 ± 4 hours (h) between applications.

Reporting group title	Diclofenac (2%) +Capsaicin (0.075%) Gel
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Reporting group description:

Patients were topically applied with Diclofenac + Capsaicin 2 g gel (40 mg diclofenac, 1.5 mg capsaicin), twice daily with 12 ± 4 hours (h) between applications.

Serious adverse events	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	0 / 223 (0.00%)	0 / 223 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Diclofenac (2%) +Capsaicin (0.075%) Gel		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 225 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo Gel	Capsaicin (0.075%) Gel	Diclofenac (2%) Gel
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 75 (5.33%)	29 / 223 (13.00%)	7 / 223 (3.14%)
General disorders and administration site conditions Burning sensation subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	16 / 223 (7.17%) 17	1 / 223 (0.45%) 1
Skin and subcutaneous tissue disorders Skin burning sensation subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	7 / 223 (3.14%) 9	2 / 223 (0.90%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	9 / 223 (4.04%) 9	4 / 223 (1.79%) 4

Non-serious adverse events	Diclofenac (2%) + Capsaicin (0.075%) Gel		
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 225 (11.56%)		
General disorders and administration site conditions Burning sensation subjects affected / exposed occurrences (all)	12 / 225 (5.33%) 15		
Skin and subcutaneous tissue disorders Skin burning sensation subjects affected / exposed occurrences (all)	12 / 225 (5.33%) 13		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	3 / 225 (1.33%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	With the introduction of this amendment, in addition to some changes in responsibilities, clarifications, correction of typographical errors, and minor revisions for consistency within the CTP or to avoid repetitions, the following changes were made: 1.The trigger point for AP was revised from ≤ 2.5 N/cm ² to ≤ 25 N/cm ² 2.The description of the formulation of study medication was changed from a semisolid formulation to a gel 3.The endpoints number of patients with a decrease in POMWP from baseline of at least 30% and 50%, respectively, to the timepoint before drug application in the morning of Day 2 (Visit 2) were revised since no POM assessment was scheduled at this timepoint 4.An analysis of the primary endpoint including an additional variable for analgesic use was added

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.

A possible limitation of this study design related to the warming effect that is attributable to the topical application of capsaicin, which could potentially have led to inadvertent unblinding of treatment assignments in the study.

Notes: