Clinical trial results:
Efficacy and safety of lidocaine 5% medicated plaster in localized chronic post-operative neuropathic pain

Summary

EudraCT number	2012-000347-28
Trial protocol	BE AT ES IT DK FR GB
Global end of trial date	21 June 2016

Results information

Result version number	v1 (current)
This version publication date	30 June 2017
First version publication date	30 June 2017

Trial information

Trial identification

Sponsor protocol code	KF10004-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1143-2130

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
Public contact	GRT Trial Information Desk, Grünenthal GmbH, +49 2415693223, Clinical-Trials@grunenthal.com
Scientific contact	GRT Trial Information Desk, Grünenthal GmbH, +49 2415693223, Clinical-Trials@grunenthal.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	11 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2016
Global end of trial reached?	Yes
Global end of trial date	21 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the superiority of the analgesic efficacy of lidocaine 5% medicated plaster in comparison to placebo in subjects with moderate to severe localized chronic post-operative neuropathic pain (PoNP).

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
The competent authorities approved the trial as required by national regulations.
Regulatory authorities were notified of the trial and amendments as required by national regulations.

Background therapy:

Allowed concomitant medications and therapies were:
Stable systemic medication (used on 5 days or more weekly) for the treatment of PoNP, e.g., antidepressants or anticonvulsants. The treatment regimen (dosage and frequency of administration) must have been stable for at east 1 month before Visit 1 (Enrollment Visit) and remained unchanged until the end of the Double-blind Treatment Period (Visit 5 [End-of-treatment Visit]) or the Discontinuation Visit.
Stable systemic medication (used on 5 days or more weekly) for any other condition that may have also affected the intensity of PoNP or perception of pain in general (e.g., antidepressants, anticonvulsants, benzodiazepines). The treatment regimen (dosage and frequency of administration) must have been stable for at least 1 month before Visit 1 and remained unchanged from Visit 1 until the end of the Double-blind Treatment Period (Visit 5 or the Discontinuation Visit).
For the treatment of acute painful conditions other than PoNP (e.g., headache) for the duration of the trial from Visit 1 until Visit 5 or the Discontinuation Visit:
− Paracetamol (not more than 3 g per day for a maximum of 3 consecutive days). The total amount was limited to 15 g per 28 days unless used for stable treatment.
OR
− Ibuprofen (not more than 1200 mg daily for a maximum of 3 consecutive days). The total amount was limited to 6 g per 28 days unless used for stable treatment.
Treatment for any other condition that did not affect the intensity of PoNP, perception of pain in general, or that did not cause PoNP.

Evidence for comparator:

N/A

Actual start date of recruitment	23 October 2012
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	Spain: 18

Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Austria: 72
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	Denmark: 41
Country: Number of subjects enrolled	France: 73
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Brazil: 68
Worldwide total number of subjects	359
EEA total number of subjects	291

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	290
From 65 to 84 years	68
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First subject signed the informed consent on the 23 October 2012 and the last subject completed the trial on the 21 June 2016.

Pre-assignment

Screening details:

A total of 444 subjects were enrolled and signed the informed consent in 42 active sites.
363 of these subjects were allocated to study drug (investigational medicinal product = IMP) and 359 subjects received IMP (180 subjects in the placebo arm, and 179 in the lidocaine arm).

Pre-assignment period milestones

Number of subjects started	444[1]
Number of subjects completed	359

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Missing: 4
Reason: Number of subjects	no IMP intake: 4
Reason: Number of subjects	Inclusion criteria not met/exclusion criterion met: 64
Reason: Number of subjects	Consent withdrawn by subject: 9
Reason: Number of subjects	Other reason: 4

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period reflects all subjects who signed an informed consent.
The worldwide number of enrolled subjects is based on the number of subjects allocated to treatment who applied any amount of IMP.

Period 1

Period 1 title	Overall trial (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:

Subjects have been randomized to receive either lidocaine 5% medicated plasters or placebo plasters. The size of the randomization blocks has not been disclosed to the investigator or any personnel involved in the conduct of the trial. The IMP has been packaged and labeled for each trial medication kit in a blinded fashion on the basis of the randomization schedule.
The placebo plaster has been visually indistinguishable from the lidocaine 5% medicated plaster.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lidocaine 5% medicated plaster

Arm description:

This arm comprises all subjects allocated to lidocaine 5% medicated plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Arm type	Experimental

Investigational medicinal product name	Lidocaine 5% medicated plaster
Investigational medicinal product code	GRT10004
Other name	
Pharmaceutical forms	Medicated plaster
Routes of administration	Topical use

Dosage and administration details:

Lidocaine 5% medicated plasters were to be applied once daily for no longer than 12 hours within 24 hours with a plaster-free period of at least 12 hours between plaster applications.
Depending on the size of the painful area, up to 3 lidocaine 5% medicated plasters could have been applied simultaneously on the painful skin.

Arm title	Matching Placebo

Arm description:

This arm comprises all subjects allocated to placebo plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

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

Dosage and administration details:

Placebo plasters were to be applied once daily for no longer than 12 hours within 24 hours with a plaster-free period of at least 12 hours between plaster applications.
Depending on the size of the painful area, up to 3 placebo plasters could have been applied simultaneously on the painful skin.

Number of subjects in period 1	Lidocaine 5% medicated plaster	Matching Placebo
Started	179	180
Completed	147	147
Not completed	32	33
Consent withdrawn by subject	3	2
Adverse event, non-fatal	7	7
Other reason	4	4
Lost to follow-up	-	1
Lack of efficacy	16	17
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Lidocaine 5% medicated plaster
Reporting group description:	
This arm comprises all subjects allocated to lidocaine 5% medicated plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).	
Reporting group title	Matching Placebo
Reporting group description:	
This arm comprises all subjects allocated to placebo plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).	

Reporting group values	Lidocaine 5% medicated plaster	Matching Placebo	Total
Number of subjects	179	180	359
Age categorical Units: Subjects			
Adults (18-64 years)	145	145	290
From 65-84 years	33	35	68
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	51.7	52.6	
standard deviation	± 14.2	± 13.5	-
Gender categorical Units: Subjects			
Female	117	114	231
Male	62	66	128
Ethnicity Units: Subjects			
Hispanic or Latino	46	42	88
Not Hispanic or Latino	121	117	238
Not Collected	12	21	33
Race Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	0	3	3
Black	4	4	8
Native Hawaiian or Other Pacific Islander	0	0	0
White	164	165	329
Not Collected	2	2	4
Other	7	4	11
Height Units: meter			
arithmetic mean	1.676	1.679	
standard deviation	± 0.093	± 0.093	-
Weight Units: kilogram(s)			

arithmetic mean	78.17	80.14	
standard deviation	± 16.26	± 17.25	-
Body Mass Index (BMI)			
Units: kilogram(s)/square meter			
arithmetic mean	27.81	28.45	
standard deviation	± 5.28	± 5.82	-

End points

End points reporting groups

Reporting group title	Lidocaine 5% medicated plaster

Reporting group description:

This arm comprises all subjects allocated to lidocaine 5% medicated plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Reporting group title	Matching Placebo

Reporting group description:

This arm comprises all subjects allocated to placebo plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Subject analysis set title	Add-on subjects_Lidocaine 5% medicated plaster
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm comprises all subjects with stable medication for the treatment of PoNP allocated to lidocaine 5% medicated plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Subject analysis set title	Add-on subjects_ Matching Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm comprises all subjects with stable medication for the treatment of PoNP allocated to placebo plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Subject analysis set title	Plaster only subjects_Lidocaine 5% medicated plaster
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm comprises all subjects without any additional medication for the treatment of PoNP allocated to lidocaine 5% medicated plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Subject analysis set title	Plaster only subjects_Matching Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm comprises all subjects without any additional medication for the treatment of PoNP allocated to placebo plaster who applied any amount of IMP and had at least 1 post-baseline 24-hour average daily pain intensity assessment on the 11-point Numeric rating scale (NRS).

Primary: Change of the 24-hours average pain intensity from baseline to week 12

End point title	Change of the 24-hours average pain intensity from baseline to week 12

End point description:

The primary efficacy endpoint was the change from baseline of the recorded average pain intensity values during the last 24 hours, averaged over the 7 days of Week 12 of the Double-blind Treatment Period.
The 24-hours pain intensity has been assessed once daily before plaster removal using an 11-point numeric rating scale where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The baseline value was defined as the calculated mean of the average pain values during the last 24 hours for the last 7 days of the Enrollment Period.
A reduction in pain intensity results in negative values.
Missing weekly average pain values have been imputed using the multiple imputation (MI) method.

End point type	Primary

End point timeframe:

Week 12

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[1]	180[2]		
Units: units on a scale				
least squares mean (standard error)	-1.7 (± 0.16)	-1.47 (± 0.16)		

Notes:

[1] - Full Analysis Set using Multiple Imputation Method

[2] - Full Analysis Set using Multiple Imputation method

Statistical analyses

Statistical analysis title	ANCOVA using Multiple imputation method (MI)

Statistical analysis description:

An analysis of covariance (ANCOVA) was performed including treatment and concomitant treatment status as factors, and the baseline pain intensity as a covariate using change from baseline on an 11-point NRS as dependent variable. Treatment effects was estimated based on least-squares means (LSmeans) of the difference between Lidocaine Plaster Arm and Placebo Arm and presented together with the corresponding 95% confidence interval (CI) and one-sided p-value for the treatment comparison.

Comparison groups	Lidocaine 5% medicated plaster v Matching Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1533 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[3] - One-sided p-value

Primary: Change of the 24-hours average pain intensity from baseline to week 12_ Subgroup analysis

End point title	Change of the 24-hours average pain intensity from baseline to week 12_ Subgroup analysis

End point description:

The primary efficacy endpoint was the change from baseline of the recorded average pain intensity values during the last 24 hours, averaged over the 7 days of Week 12 of the Double-blind Treatment Period.
The 24-hours pain intensity has been assessed once daily before plaster removal using an 11-point numeric rating scale where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The baseline value was defined as the calculated mean of the average pain values during the last 24 hours for the last 7 days of the Enrollment Period.
Missing weekly average pain values have been imputed using the multiple imputation (MI) method.

End point type	Primary

End point timeframe:

Week 12

End point values	Add-on subjects_Lidocaine 5% medicated plaster	Add-on subjects_ Matching Placebo	Plaster only subjects_Lidocaine 5% medicated plaster	Plaster only subjects_Matching Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91[4]	96[5]	88[6]	84[7]
Units: units on a scale				
least squares mean (standard error)	-1.56 (± 0.23)	-1.55 (± 0.22)	-1.87 (± 0.23)	-1.36 (± 0.24)

Notes:

[4] - Subgroup of the Full Analysis Set using Multiple Imputation Method

[5] - Subgroup of the Full Analysis Set using Multiple Imputation Method

[6] - Subgroup of the Full Analysis Set using Multiple Imputation Method

[7] - Subgroup of the Full Analysis Set using Multiple Imputation Method

Statistical analyses

Statistical analysis title	ANCOVA using MI method_ Add-on subjects

Statistical analysis description:

An analysis of covariance (ANCOVA) was performed including treatment and concomitant treatment status as factors, and the baseline pain intensity as a covariate using change from baseline on an 11-point NRS as dependent variable. Treatment effects was estimated based on least-squares means (LSmeans) of the difference between Lidocaine Plaster Arm and Placebo Arm and presented together with the corresponding 95% confidence interval (CI) for the treatment comparison.

Comparison groups	Add-on subjects_Lidocaine 5% medicated plaster v Add-on subjects_ Matching Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	ANCOVA using MI method_ Plaster only subjects

Statistical analysis description:

An analysis of covariance (ANCOVA) was performed including treatment and concomitant treatment status as factors, and the baseline pain intensity as a covariate using change from baseline on an 11-point NRS as dependent variable. Treatment effects was estimated based on least-squares means (LSmeans) of the difference between Lidocaine Plaster Arm and Placebo Arm and presented together

with the corresponding 95% confidence interval (CI) for the treatment comparison.

Comparison groups	Plaster only subjects_Lidocaine 5% medicated plaster v Plaster only subjects_Matching Placebo
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.33

Secondary: Mean pain intensity and mean pain intensity change from baseline based on the 24-hour average pain intensity

End point title	Mean pain intensity and mean pain intensity change from baseline based on the 24-hour average pain intensity

End point description:

Mean pain intensity and mean pain intensity change from baseline based on the average pain intensity during the last 24 hours, calculated over the last 28 days (4 weeks) and 84 days (12 weeks) of the Double-blind Treatment Period.
The subject scored their average pain intensity during the last 24 hours on an 11-point NRS where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine".
The pain intensity has been assessed once daily before plaster removal.
Mean pain intensity and mean pain intensity change from baseline have been summarized descriptively.

End point type	Secondary

End point timeframe:

The last 28 days (4 weeks) and 84 days (12 weeks) of the Double-blind Treatment Period.

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[8]	180[9]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 179; N = 180)	6.66 (± 1.41)	6.47 (± 1.38)		
Averaged over the last 4 weeks (N = 143; N = 141)	5 (± 2.25)	4.97 (± 2.45)		
Averaged over the 12 weeks (N = 151; N = 156)	5.4 (± 1.88)	5.31 (± 2.06)		
Change to 4 weeks average (N =143; N =141)	-1.61 (± 2.02)	-1.49 (± 2.07)		
Change to 12 weeks average (N =151; N =156)	-1.22 (± 1.55)	-1.14 (± 1.58)		

Notes:

[8] - Full Analysis Set

[9] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Mean pain intensity and mean pain intensity change from baseline based on the current pain intensity

End point title	Mean pain intensity and mean pain intensity change from baseline based on the current pain intensity

End point description:

Mean pain intensity and mean pain intensity change from baseline based on the current pain intensity before plaster removal, calculated over the last 7 days, 28 days (4 weeks), and 84 days (12 weeks) of the Double-blind Treatment Period.
The subject scored their current pain intensity on an 11-point NRS where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine".
The current pain intensity before plaster removal has been assessed once daily.
Mean pain intensity and mean pain intensity change from baseline have been summarized descriptively.

End point type	Secondary

End point timeframe:

Last 7 days, 28 days (4 weeks), and 84 days (12 weeks) of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[10]	180[11]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N =179; N = 180)	6.46 (± 1.56)	6.34 (± 1.5)		
Averaged over the last week (N =122; N =115)	4.56 (± 2.4)	4.96 (± 2.55)		
Averaged over the last 4 weeks (N =133; N =127)	4.65 (± 2.33)	4.9 (± 2.51)		
Averaged over the 12 weeks (N =140; N =141)	4.95 (± 1.97)	5.18 (± 2.22)		
Change to last week average (N =122; N =115)	-1.88 (± 2.23)	-1.48 (± 1.94)		
Change to 4 weeks average (N =133; N =127)	-1.75 (± 2.11)	-1.48 (± 1.98)		
Change to 12 weeks average (N =140; N =141)	-1.43 (± 1.64)	-1.23 (± 1.64)		

Notes:

[10] - Full Analysis Set

[11] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly mean pain intensities and weekly mean pain intensity change from baseline based on the 24-hour average pain intensity before plaster removal

End point title	Weekly mean pain intensities and weekly mean pain intensity change from baseline based on the 24-hour average pain intensity before plaster removal

End point description:

Weekly mean pain intensities and weekly mean pain intensity change from baseline based on the 24-hour average pain intensity calculated for each of the 12 weeks of the Double-blind Treatment Period.
Pain intensity has been assessed once daily before plaster removal.
The subject scored their pain intensity on an 11-point Numerical Rating Scale (NRS) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine".
Mean pain intensity and weekly mean pain intensity change from baseline have been summarized descriptively.

End point type	Secondary

End point timeframe:

Each of the 12 weeks of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[12]	180[13]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 179; N = 180)	6.66 (± 1.41)	6.47 (± 1.38)		
Week 1 (N= 170; N= 175)	6.16 (± 1.59)	6 (± 1.59)		
Week 2 (N= 168; N= 169)	5.88 (± 1.76)	5.69 (± 1.82)		
Week 3 (N= 164; N= 171)	5.71 (± 1.91)	5.54 (± 2)		
Week 4 (N= 158; N= 167)	5.53 (± 2.02)	5.46 (± 2.05)		
Week 5 (N= 157; N= 159)	5.46 (± 2)	5.36 (± 2.17)		
Week 6 (N= 147; N= 155)	5.39 (± 2.01)	5.27 (± 2.28)		
Week 7 (N= 144; N=147)	5.3 (± 2.09)	5.21 (± 2.28)		
Week 8 (N= 145; N= 150)	5.3 (± 2.17)	5.18 (± 2.39)		
Week 9 (N= 140; N= 142)	5.18 (± 2.29)	5.11 (± 2.42)		
Week 10 (N= 141; N= 140)	5.02 (± 2.31)	5.11 (± 2.43)		
Week 11 (N= 137; N= 135)	5.06 (± 2.31)	4.97 (± 2.51)		
Week 12 (N= 129; N= 130)	4.88 (± 2.32)	4.94 (± 2.52)		
Change from baseline to week 1 (N= 170; N= 175)	-0.48 (± 1.01)	-0.45 (± 1.01)		
Change from baseline to week 2 (N= 168; N=169)	-0.75 (± 1.24)	-0.74 (± 1.28)		
Change from baseline to week 3 (N= 164; N=171)	-0.95 (± 1.54)	-0.9 (± 1.47)		
Change from baseline to week 4 (N= 158; N= 167)	-1.13 (± 1.75)	-0.98 (± 1.56)		
Change from baseline to week 5 (N= 157; N=159)	-1.15 (± 1.73)	-1.12 (± 1.71)		
Change from baseline to week 6 (N= 147; N= 155)	-1.26 (± 1.8)	-1.17 (± 1.88)		
Change from baseline to week 7 (N= 144; N= 147)	-1.39 (± 1.88)	-1.27 (± 1.82)		
Change from baseline to week 8 (N= 145; N= 150)	-1.36 (± 1.93)	-1.32 (± 1.92)		

Change from baseline to week 9 (N= 140; N= 142)	-1.51 (± 2.03)	-1.37 (± 1.99)		
Change from baseline to week 10 (N= 141; N=140)	-1.6 (± 2.1)	-1.39 (± 2.08)		
Change from baseline to week 11 (N= 137; N= 135)	-1.57 (± 2.08)	-1.48 (± 2.1)		
Change from baseline to Week 12 (N= 129; N= 130)	-1.78 (± 2.15)	-1.54 (± 2.11)		

Notes:

[12] - Full Analysis Set

[13] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly mean pain intensities and weekly mean pain intensity change based on current pain intensity before plaster removal

End point title	Weekly mean pain intensities and weekly mean pain intensity change based on current pain intensity before plaster removal

End point description:

Weekly mean pain intensities and weekly mean pain intensity change from baseline based on the current pain intensity before plaster removal calculated for each of the 12 weeks of the Double-blind Treatment Period.
The subject scored their current pain intensity on an 11-point Numerical Rating Scale (NRS) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine".
The current pain intensity has been assessed once daily before plaster removal.
Mean pain intensity and weekly mean pain intensity change from baseline have been summarized descriptively.

End point type	Secondary

End point timeframe:

Each of the 12 weeks of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[14]	180[15]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 179; N = 180)	6.46 (± 1.56)	6.34 (± 1.5)		
Week 1 (N= 158; N= 161)	5.73 (± 1.82)	5.77 (± 1.75)		
Week 2 (N= 154; N= 152)	5.47 (± 1.96)	5.46 (± 1.99)		
Week 3 (N= 154; N= 159)	5.2 (± 2.07)	5.37 (± 2.12)		
Week 4 (N= 148; N= 155)	5.08 (± 2.18)	5.26 (± 2.19)		
Week 5 (N= 142; N= 144)	5.11 (± 2.05)	5.27 (± 2.24)		
Week 6 (N= 134; N= 141)	4.98 (± 2.11)	5.18 (± 2.32)		
Week 7 (N= 131; N=134)	4.95 (± 2.24)	5.09 (± 2.42)		
Week 8 (N= 133; N= 139)	4.92 (± 2.28)	5.08 (± 2.43)		
Week 9 (N= 127; N= 132)	4.81 (± 2.36)	5.04 (± 2.46)		
Week 10 (N= 131; N= 127)	4.59 (± 2.36)	5.02 (± 2.48)		
Week 11 (N= 126; N= 123)	4.57 (± 2.41)	4.86 (± 2.58)		
Week 12 (N= 122; N= 115)	4.56 (± 2.4)	4.96 (± 2.55)		

Change from baseline to week 1 (N= 158; N= 161)	-0.73 (± 1.21)	-0.57 (± 1.18)		
Change from baseline to week 2 (N= 154; N= 152)	-0.97 (± 1.42)	-0.89 (± 1.45)		
Change from baseline to week 3 (N= 154; N= 159)	-1.24 (± 1.61)	-1.03 (± 1.54)		
Change from baseline to week 4 (N= 148; N= 155)	-1.36 (± 1.85)	-1.12 (± 1.6)		
Change from baseline to week 5 (N= 142; N= 144)	-1.32 (± 1.85)	-1.16 (± 1.7)		
Change from baseline to week 6 (N= 134; N=141)	-1.4 (± 1.9)	-1.2 (± 1.87)		
Change from baseline to week 7 (N= 131; N= 134)	-1.5 (± 2.04)	-1.33 (± 1.88)		
Change from baseline to week 8 (N= 133; N= 139)	-1.53 (± 2.12)	-1.33 (± 1.91)		
Change from baseline to week 9 (N= 127; N= 132)	-1.62 (± 2.09)	-1.38 (± 1.92)		
Change from baseline to week 10 (N= 131; N= 127)	-1.78 (± 2.18)	-1.42 (± 1.99)		
Change from baseline to week 11 (N= 126; N= 123)	-1.84 (± 2.22)	-1.51 (± 2.03)		
Change from baseline to week 12 (N= 122; N= 115)	-1.88 (± 2.23)	-1.48 (± 1.94)		

Notes:

[14] - Full Analysis Set

[15] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rates based on average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period

End point title	Responder rates based on average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period

End point description:

The percentage change from baseline of the average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period has been calculated for each subject.
Responders are defined as subjects with at least 30% or 50% reduction. All discontinued subjects were considered non-responders except for those who did not require pain treatment any more due to absence of pain.
Responder rates (thresholds of 30% and 50% improvement compared to baseline) have been descriptively summarized.

End point type	Secondary

End point timeframe:

The last 24 hours at the end of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[16]	180[17]		
Units: subjects				

Responder with more or equal of 30% pain reduction	41	45		
Responder with more or equal of 50% pain reduction	13	19		

Notes:

[16] - Full Analysis Set

[17] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Final score of the painDETECT Pain Questionnaire and the changes from baseline during the Double-blind Treatment Period

End point title	Final score of the painDETECT Pain Questionnaire and the changes from baseline during the Double-blind Treatment Period

End point description:

The painDETECT questionnaire was specifically developed to detect neuropathic pain components in adult patients with low back pain.
The questionnaire consists of seven questions that address the quality of neuropathic pain symptoms with a final score between zero and 38.
A higher score shows more likelihood of a neuropathic pain component.
The final score and the changes from baseline during the Double-blind Treatment Period have been summarized.

End point type	Secondary

End point timeframe:

Visit 3 (week 4), visit 4 (week 8) and visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period.

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[18]	180[19]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N =177; N = 180)	20.8 (± 5.3)	21.5 (± 5.6)		
Visit 3 (N= 157; N= 160)	17.8 (± 7)	18.1 (± 7)		
Visit 4 (N= 145; N= 146)	16.9 (± 7.3)	16.8 (± 7.7)		
Visit 5 (N= 174; N= 167)	16.4 (± 8)	16.6 (± 8.3)		
Change from baseline to visit 3 (N= 157; N= 160)	-2.9 (± 5.2)	-3.4 (± 5)		
Change from baseline to visit 4 (N= 145; N= 146)	-3.9 (± 5.7)	-4.9 (± 6.2)		
Change from baseline to visit 5 (N= 174; N= 167)	-4.4 (± 6.3)	-5 (± 6.7)		

Notes:

[18] - Full Analysis Set

[19] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity from mechanical dynamic allodynia (brush) testing and change from baseline

End point title	Pain intensity from mechanical dynamic allodynia (brush) testing and change from baseline

End point description:

The test has been conducted by means of a brush provided by the sponsor. The skin in PoNP area has been repeatedly lightly stroked with a brush with an interval of more than 5 seconds between the strokes. The intensity of the pain has been assessed by subject and the highest severity of the pain has been rated using the 11-point NRS.
Pain intensity from mechanical dynamic allodynia (brush) testing and change from baseline has been summarized.

End point type	Secondary

End point timeframe:

Visit 3 (week 4), visit 4 (week 8) and visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[20]	180[21]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N= 178; N= 180)	6.2 (± 2.1)	6.1 (± 2.3)		
Visit 3 (N= 159; N= 164)	4.8 (± 2.4)	4.9 (± 2.6)		
Visit 4 (N= 146; N= 148)	4.7 (± 2.7)	4.6 (± 2.8)		
Visit 5 (N= 175; N= 176)	4.7 (± 2.7)	4.7 (± 2.8)		
Change from baseline to visit 3 (N= 158; N= 164)	-1.3 (± 2.2)	-1.2 (± 2)		
Change from baseline to visit 4 (N= 145; N= 148)	-1.5 (± 2.5)	-1.6 (± 2.7)		
Change from baseline to visit 5 (N= 174; N=176)	-1.5 (± 2.6)	-1.3 (± 2.5)		

Notes:

[20] - Full Analysis Set

[21] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Anxiety and depression scores of HADS and changes from baseline

End point title	Anxiety and depression scores of HADS and changes from baseline

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment scale for detecting states of depression and anxiety.
It contains 2 subscales, one for anxiety and one for depression, each consisting of 7 items.
Each subscale consists of 7 statements, rated on a scale of 0 to 3 (0 = No anxiety or depression, to 3 = Severe feelings of anxiety or depression), resulting in a range for each dimension from 0-21. Higher scores denote greater severity of depression or anxiety.
The 2 subscores have been calculated as the sum of corresponding items

End point type	Secondary

End point timeframe:

Visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170[22]	180[23]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Anxiety_ Baseline (N=178; N= 178)	8.8 (± 4.5)	9.3 (± 4.8)		
Anxiety_Visit 5 (N=174; N= 172)	7.7 (± 4.7)	8 (± 4.8)		
Anxiety_ Change from baseline (N=174; N=170)	-1.1 (± 3.5)	-1.3 (± 3.2)		
Depression_ Baseline (N=178, N=178)	7 (± 4.2)	7.6 (± 4.5)		
Depression_V5 (N=174; N=172)	6.3 (± 4.4)	7.1 (± 4.7)		
Depression_ Change from baseline (N=174; N=170)	-0.7 (± 3.3)	-0.5 (± 3.3)		

Notes:

[22] - Full Analysis Set

[23] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Rating of global improvement and satisfaction with treatment according to PGIC

End point title	Rating of global improvement and satisfaction with treatment according to PGIC

End point description:

Subjects rated their global improvement and satisfaction with treatment on a 7-point scale that ranges from “very much improved” to “very much worse” with “no change” as the mid-point.
The results have been summarized.

End point type	Secondary

End point timeframe:

Visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[24]	180[25]		
Units: subjects				
Not Done	4	6		
Very much improved	11	20		
Much improved	52	42		
Minimally improved	47	40		
No change	49	55		

Minimally worse	11	12		
Much worse	5	4		
Very much worse	0	0		
Missing	0	1		

Notes:

[24] - Full Analysis Set

[25] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: The weighted Health Status Index of quality of life by means of EuroQol-5 Dimension

End point title	The weighted Health Status Index of quality of life by means of EuroQol-5 Dimension

End point description:

The EQ 5D Health Questionnaire is a generic health related quality of life instrument which can be used in the clinical and economic evaluation of healthcare and in population health surveys to assess health outcome from a wide variety of interventions.
The EQ-5D has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has been scored as followed: no problems = 1, some problems = 2, and extreme problems = 3.
A higher score in the Weighted Health Status Index indicates an improvement in health.

End point type	Secondary

End point timeframe:

Visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period.

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[26]	180[27]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N= 178; N= 178)	0.397 (± 0.321)	0.392 (± 0.334)		
Visit 5 (N= 175; N= 169)	0.497 (± 0.313)	0.495 (± 0.322)		
Change from baseline to visit 5 (N= 174; N= 167)	0.098 (± 0.282)	0.107 (± 0.281)		

Notes:

[26] - Full Analysis Set

[27] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Total score in quality of sleep using CPSI and change from baseline

End point title	Total score in quality of sleep using CPSI and change from baseline

End point description:

The Impact of pain on sleep quality has been assessed by the Chronic Pain Sleep Inventory (CPSI). The CPSI consists of 5 items which measure trouble falling asleep, needing sleep medication, awakened by pain during the night and in the morning, and overall quality of sleep on a 100 mm visual analog scale. The total score and change from baseline have been summarized descriptively.
A higher score indicates more sleeping problems.

End point type	Secondary

End point timeframe:

Visit 5 (week 12; End-of treatment/Discontinuation Visit) of the Double blind Treatment Period

End point values	Lidocaine 5% medicated plaster	Matching Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[28]	180[29]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Sleep Problem Index Baseline (N = 176; N = 179)	161.9 (± 86.9)	153.4 (± 89.8)		
Sleep Problem Index Visit 5 (N= 173; N= 171)	122.8 (± 89.6)	110.1 (± 95.5)		
Change from baseline to visit 5 (N= 170; N= 170)	-38.7 (± 78.4)	-43.3 (± 91.2)		

Notes:

[28] - Full Analysis Set

[29] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rates based on average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period__ Subgroup analysis

End point title	Responder rates based on average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period__ Subgroup analysis

End point description:

The percentage change from baseline of the average pain intensity values during the last 24 hours at the end of the Double-blind Treatment Period has been calculated for each subject.
Responders are defined as subjects with at least 30% or 50% reduction. All discontinued subjects were considered non-responders except for those who did not require pain treatment any more due to absence of pain.
Responder rates (thresholds of 30% and 50% improvement compared to baseline) have been descriptively summarized.

End point type	Secondary

End point timeframe:

The last 24 hours at the end of the Double blind Treatment Period

End point values	Add-on subjects_Lidocaine 5% medicated plaster	Add-on subjects_ Matching Placebo	Plaster only subjects_Lidocaine 5% medicated plaster	Plaster only subjects_Matching Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91[30]	96[31]	88[32]	84[33]
Units: Subjects				
Responder with more or equal of 30% pain reduction	19	26	22	19
Responder with more or equal of 50% pain reduction	8	12	5	7

Notes:

[30] - Subgroup of the Full Analysis Set

[31] - Subgroup of the Full Analysis Set

[32] - Subgroup of the Full Analysis Set

[33] - Subgroup of the Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events (TEAEs) reported include all Adverse Events occuring after first application of investigational medicinal product (IMP) up to and including Visit 6 (end of double-blind treatment, i.e. up to 12 weeks).

Adverse event reporting additional description:

Events present at enrollment were considered medical history. Events that worsened between enrollment and first application of plaster were Adverse Events, but not Treatment Emergent Adverse Events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Lidocaine 5% medicated plaster

Reporting group description:

This arm comprises all subjects allocated to lidocaine 5% medicated plaster who applied any amount of IMP.
Subjects were analyzed as administered, i.e., based on actual treatment received.

Reporting group title	Matching Placebo

Reporting group description:

This arm comprises all subjects allocated to placebo plaster who applied any amount of IMP.
Subjects were analyzed as administered, i.e., based on actual treatment received.

Serious adverse events	Lidocaine 5% medicated plaster	Matching Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 179 (3.35%)	5 / 180 (2.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Thoracic vertebral fracture	Additional description: verbatim text: Thoracic vertebral fracture TH11		
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			

subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	2 / 179 (1.12%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 179 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis	Additional description: verbatim text: shock wave therapy right shoulder		
subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	1 / 179 (0.56%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lidocaine 5% medicated plaster	Matching Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 179 (12.85%)	15 / 180 (8.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 179 (5.59%)	8 / 180 (4.44%)	
occurrences (all)	13	8	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	13 / 179 (7.26%)	7 / 180 (3.89%)	
occurrences (all)	13	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2014	This amendment was mainly issued to modify inclusion/exclusion criteria and to specify further the reporting requirements for medical history. Furthermore, for the analysis of the primary endpoint and the definition of the analysis populations, the wording changes were necessary for clarity. In addition, the planned sensitivity analyses were changed to comply with recommendations given in The National Academy of Sciences report on "The Prevention and Treatment of Missing Data in Clinical Trials" commissioned by the FDA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported