Clinical trial results:
An exploratory, randomized, double-blind, double-dummy, placebo- and active-controlled Phase II trial to evaluate the efficacy and safety of a topical application of GRT7019 in subjects with chronic pain due to knee osteoarthritis

Summary

EudraCT number	2016-002611-18
Trial protocol	AT DE ES
Global end of trial date	17 January 2018

Results information

Result version number	v1 (current)
This version publication date	17 October 2018
First version publication date	17 October 2018

Trial information

Trial identification

Sponsor protocol code	KF7019-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1184-3912

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 0049 2415693223, Clinical-Trials@grunenthal.com
Scientific contact	Dr. Irmgard Bösl, Grünenthal GmbH, 0049 2415690, 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	13 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the analgesic efficacy of a once daily application of GRT7019 for 4 weeks compared to placebo.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws and regulations, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory authorities were notified of the trial as required by national regulations, and where necessary relevant authorization was obtained.

Background therapy:

Allowed concomitant treatments included:
Acetylsalicylic acid (oral doses less than or equal to 325 mg per day for cardiac prophylaxis).

Hypnotics including benzodiazepines and non-benzodiazepines if previously used regularly according to the respective Summary of Product Characteristics (SmPCs) for at least 4 weeks prior to the Enrollment Visit and planned to continue on the same dose regimen throughout the trial.

Selective serotonin reuptake inhibitors for the treatment of stable depression if previously used at a controlled, stable dose for at least 3 months prior to Enrollment Visit.

Triptans for the treatment of migraine.

Transcutaneous electrical nerve stimulation, acupuncture, and other physiotherapy, packs and massages, and psychological support were allowed during the trial, provided that the subjects had been on that therapy for at least 4 weeks prior to the Enrollment Visit and continued to undergo that therapy for the duration of the trials at the same frequency and intensity as before. Packs were only allowed if they did not apply external heat to the subject.

For unacceptable pain due to chronic osteoarthritis during the trial, paracetamol tablets (500 mg) were provided as rescue medication to all treatment groups. No rescue medication was allowed during the last 3 days before the Baseline Visit. The maximum total daily dose of paracetamol was 2000 mg during the Washout Phase and after allocation to trial treatment until the Follow-up Visit. During the Treatment Period, paracetamol was not be taken for more than 3 consecutive days at the maximum allowed total daily dose.

In the subjects randomized to the diclofenac treatment arm, over-encapsulated pantoprazole 20-mg tablets were provided once daily to prevent gastrointestinal system related injuries/bleeding that could result from the treatment with oral diclofenac.

Evidence for comparator:

Diclofenac, an approved drug indicated for use in chronic pain due to osteoarthritis (OA) and recommended in treatment guidelines for OA (McAlindon et al. 2014, American Academy of Orthopaedic Surgeons 2013, Jordan et al. 2003), was selected as active comparator/standard of care to demonstrate assay sensitivity. The use of NSAIDs is also in line with The National Institute for Health and Care Excellence (NICE) recommendations for the pharmacological treatment of OA (NICE 2014).
A lidocaine patch (Versatis®) was selected as comparator to fulfill in part the requirements of the draft Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/281825/2015) to test the efficacy and show the tolerability profile of the individual component.

Actual start date of recruitment	12 June 2017
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	Poland: 29
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Germany: 116
Country: Number of subjects enrolled	Spain: 26
Worldwide total number of subjects	185
EEA total number of subjects	185

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)	117
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 229 subjects signed an informed consent at 29 active sites. 185 of these subjects were allocated to study drug (investigational medicinal product = IMP) and received IMP (46 subjects in the placebo arm, 46 in the GRT7019 arm, 48 in the diclofenac arm, and 45 in the lidocaine topical patch arm).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	229[1]
Number of subjects completed	185

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 10
Reason: Number of subjects	Failure to meet randomization criteria: 31
Reason: Number of subjects	Technical reason: 1
Reason: Number of subjects	Other: 1

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: 229 subjects signed an informed consent. 185 subjects received at least one dose of investigational medicinal product.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo patches (matching GRT7019 and lidocaine 5% medicated plasters) and placebo capsules (matching over-encapsulated diclofenac sodium tablets)

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

Dosage and administration details:

All IMPs were administered in a double-dummy design to maintain the blinding. A placebo patch (matching GRT7019 and lidocaine 5% medicated plaster) was administered once daily for 4 weeks with a wearing time of up to 18 hours but not less than 11 hours. Placebo patches, approximately 14 x 10 cm, should have been administered in the morning at a time suitable to accommodate the subjects' needs and had to be fixed at the bent knee with an elastic mesh bandage. Placebo capsules matching the over-encapsulated diclofenac tablets were administered twice daily, i.e., in the morning (before a meal) and in the evening, for 4 weeks. A placebo capsule matching pantoprazole tablets was taken once

daily in the morning for 4 weeks.

Arm title	GRT7019

Arm description:

A fixed-dose combination patch containing 5% lidocaine (700 mg) and 1.3% diclofenac epolamine (182 mg)

Arm type	Experimental
Investigational medicinal product name	GRT7019
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicated plaster
Routes of administration	Topical use

Dosage and administration details:

All IMPs were administered in a double-dummy design to maintain the blinding. GRT7019 patches were administered once daily for 4 weeks with a wearing time of up to 18 hours but not less than 11 hours. The patches, approximately 14 x 10 cm, should have been administered in the morning at a time suitable to accommodate the subjects' needs and had to be fixed at the bent knee with an elastic mesh bandage. Placebo capsules matching the over-encapsulated diclofenac tablets were administered twice daily, i.e., in the morning (before a meal) and in the evening, for 4 weeks. A placebo capsule matching pantoprazole tablets was taken once daily in the morning for 4 weeks.

Arm title	Diclofenac

Arm description:

Over-encapsulated diclofenac sodium sustained-release (62.5 mg)/immediate-release (12.5 mg) tablets.

Arm type	Active comparator
Investigational medicinal product name	Diclofenac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All IMPs were administered in a double-dummy design to maintain the blinding. A diclofenac capsule (containing 62.5 mg sustained-release and 12.5 mg immediate-release diclofenac sodium) was administered orally twice daily, i.e., in the morning (before a meal) and in the evening, for 4 weeks. Over-encapsulated pantoprazole 20-mg tablets were taken once daily to prevent gastrointestinal system related injuries/bleeding that could result from the treatment with oral diclofenac. A placebo patch (matching GRT7019 and lidocaine 5% medicated plaster) was administered once daily for 4 weeks with a wearing time of up to 18 hours but not less than 11 hours. Placebo patches should have been administered in the morning at a time suitable to accommodate the subjects' needs and must be fixed at the bent knee with an elastic mesh bandage.

Arm title	Lidocaine 5% medicated plaster

Arm description:

Versatis® (lidocaine 5% medicated plaster, containing 700 mg lidocaine)

Arm type	Active comparator
Investigational medicinal product name	Lidocaine 5% medicated plaster
Investigational medicinal product code	
Other name	Versatis
Pharmaceutical forms	Medicated plaster
Routes of administration	Topical use

Dosage and administration details:

Lidocaine 5% medicated plasters were applied once daily for 4 weeks with a wearing time of up to 18 hours and a minimum wearing time of 11 hours. Patches should have been administered in the morning to accommodate the subject's needs and were required to be fixed at the bent knee with an elastic

mesh bandage. Placebo capsules matching the over-encapsulated diclofenac tablets were administered twice daily, i.e., in the morning (before a meal) and in the evening, for 4 weeks. A placebo capsule matching pantoprazole tablets was taken once daily in the morning for 4 weeks.

Number of subjects in period 1	Placebo	GRT7019	Diclofenac
Started	46	46	48
Completed	41	42	39
Not completed	5	4	9
Consent withdrawn by subject	-	2	3
Adverse event, non-fatal	2	1	2
Missing	2	-	2
Technical reason	-	-	1
Protocol deviation	1	1	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Lidocaine 5% medicated plaster
Started	45
Completed	42
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Missing	2
Technical reason	-
Protocol deviation	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo patches (matching GRT7019 and lidocaine 5% medicated plasters) and placebo capsules (matching over-encapsulated diclofenac sodium tablets)	
Reporting group title	GRT7019
Reporting group description:	
A fixed-dose combination patch containing 5% lidocaine (700 mg) and 1.3% diclofenac epolamine (182 mg)	
Reporting group title	Diclofenac
Reporting group description:	
Over-encapsulated diclofenac sodium sustained-release (62.5 mg)/immediate-release (12.5 mg) tablets.	
Reporting group title	Lidocaine 5% medicated plaster
Reporting group description:	
Versatis® (lidocaine 5% medicated plaster, containing 700 mg lidocaine)	

Reporting group values	Placebo	GRT7019	Diclofenac
Number of subjects	46	46	48
Age categorical Units: Subjects			
Adults (18-64 years)	31	26	29
Adults (65-84 years)	15	20	19
Age continuous Units: years			
arithmetic mean	61.2	63.4	61.2
standard deviation	± 8.0	± 7.5	± 8.6
Gender categorical Units: Subjects			
Female	27	30	36
Male	19	16	12
Race Units: Subjects			
White	45	46	48
American Indian or Alaska Native	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Height Units: meter			
arithmetic mean	1.707	1.68	1.672
standard deviation	± 0.089	± 0.095	± 0.08
Weight Units: kilogram(s)			
arithmetic mean	83.1	83.1	83.0
standard deviation	± 13.9	± 13.6	± 12.3
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	28.4	29.3	29.8
standard deviation	± 3.6	± 3.5	± 4.2

WOMAC index score			
The WOMAC index score was calculated for the Full Analysis Set by summarizing the scores for the pain, stiffness and physical function subscales (as described by McConnel S, Kolopack P, Davis AM. The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 2001; 45(5):453-61.)			
Units: units on a scale			
arithmetic mean	NA	NA	NA
standard deviation	±	±	±
Baseline pain intensity			
Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the morning value of Day 1). Pain intensities were assessed by the subject in an eDiary twice daily (in the morning and the evening) using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine).			
Units: units on a scale			
arithmetic mean	NA	NA	NA
standard deviation	±	±	±
History of osteoarthritis			
Answer to the question: "When were you diagnosed with OA of the knee?"			
Units: years			
arithmetic mean	9.0	9.7	11.5
standard deviation	± 8.4	± 8.3	± 10.8

Reporting group values	Lidocaine 5% medicated plaster	Total	
Number of subjects	45	185	
Age categorical			
Units: Subjects			
Adults (18-64 years)	31	117	
Adults (65-84 years)	14	68	
Age continuous			
Units: years			
arithmetic mean	60.7		
standard deviation	± 9.0	-	
Gender categorical			
Units: Subjects			
Female	28	121	
Male	17	64	
Race			
Units: Subjects			
White	44	183	
American Indian or Alaska Native	0	1	
Native Hawaiian or Other Pacific Islander	1	1	
Height			
Units: meter			
arithmetic mean	1.708		
standard deviation	± 0.091	-	
Weight			
Units: kilogram(s)			
arithmetic mean	83.1		
standard deviation	± 15.4	-	
Body Mass Index			
Units: kilogram(s)/square meter			

arithmetic mean	28.4		
standard deviation	± 3.7	-	
WOMAC index score			
The WOMAC index score was calculated for the Full Analysis Set by summarizing the scores for the pain, stiffness and physical function subscales (as described by McConnel S, Kolopack P, Davis AM. The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 2001; 45(5):453-61.)			
Units: units on a scale			
arithmetic mean	NA		
standard deviation	±	-	
Baseline pain intensity			
Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the morning value of Day 1). Pain intensities were assessed by the subject in an eDiary twice daily (in the morning and the evening) using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine).			
Units: units on a scale			
arithmetic mean	NA		
standard deviation	±	-	
History of osteoarthritis			
Answer to the question: "When were you diagnosed with OA of the knee?"			
Units: years			
arithmetic mean	11.0		
standard deviation	± 9.8	-	

Subject analysis sets

Subject analysis set title	Placebo FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	GRT7019 FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	Diclofenac FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	Lidocaine 5% medicated plaster FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	

Reporting group values	Placebo FAS	GRT7019 FAS	Diclofenac FAS
Number of subjects	46	45	47
Age categorical			
Units: Subjects			
Adults (18-64 years)	31	26	29
Adults (65-84 years)	15	19	18

Age continuous Units: years			
arithmetic mean	61.2	63.3	61.0
standard deviation	± 8.0	± 7.5	± 8.7
Gender categorical Units: Subjects			
Female	27	29	35
Male	19	16	12
Race Units: Subjects			
White	46	45	47
American Indian or Alaska Native	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Height Units: meter			
arithmetic mean	170.7	168.0	167.3
standard deviation	± 8.9	± 9.6	± 8.1
Weight Units: kilogram(s)			
arithmetic mean	83.1	83.4	83.2
standard deviation	± 13.9	± 13.5	± 12.4
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	28.4	29.5	29.8
standard deviation	± 3.6	± 3.5	± 4.3
WOMAC index score			
The WOMAC index score was calculated for the Full Analysis Set by summarizing the scores for the pain, stiffness and physical function subscales (as described by McConnel S, Kolopack P, Davis AM. The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 2001; 45(5):453-61.)			
Units: units on a scale			
arithmetic mean	50.9	43.5	48.7
standard deviation	± 11.3	± 12.5	± 11.0
Baseline pain intensity			
Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the morning value of Day 1). Pain intensities were assessed by the subject in an eDiary twice daily (in the morning and the evening) using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine).			
Units: units on a scale			
arithmetic mean	5.76	5.59	5.55
standard deviation	± 0.93	± 0.90	± 0.78
History of osteoarthritis			
Answer to the question: "When were you diagnosed with OA of the knee?"			
Units: years			
arithmetic mean	NA	NA	NA
standard deviation	±	±	±

Reporting group values	Lidocaine 5% medicated plaster FAS		
Number of subjects	45		

Age categorical Units: Subjects			
Adults (18-64 years)	31		
Adults (65-84 years)	14		
Age continuous Units: years			
arithmetic mean	60.7		
standard deviation	± 9.0		
Gender categorical Units: Subjects			
Female	28		
Male	17		
Race Units: Subjects			
White	44		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	1		
Height Units: meter			
arithmetic mean	170.8		
standard deviation	± 9.1		
Weight Units: kilogram(s)			
arithmetic mean	83.1		
standard deviation	± 15.4		
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	28.4		
standard deviation	± 3.7		
WOMAC index score			
The WOMAC index score was calculated for the Full Analysis Set by summarizing the scores for the pain, stiffness and physical function subscales (as described by McConnel S, Kolopack P, Davis AM. The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 2001; 45(5):453-61.)			
Units: units on a scale			
arithmetic mean	49.7		
standard deviation	± 11.0		
Baseline pain intensity			
Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the morning value of Day 1). Pain intensities were assessed by the subject in an eDiary twice daily (in the morning and the evening) using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine).			
Units: units on a scale			
arithmetic mean	5.69		
standard deviation	± 0.98		
History of osteoarthritis			
Answer to the question: "When were you diagnosed with OA of the knee?"			
Units: years			
arithmetic mean	NA		
standard deviation	±		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo patches (matching GRT7019 and lidocaine 5% medicated plasters) and placebo capsules (matching over-encapsulated diclofenac sodium tablets)	
Reporting group title	GRT7019
Reporting group description:	
A fixed-dose combination patch containing 5% lidocaine (700 mg) and 1.3% diclofenac epolamine (182 mg)	
Reporting group title	Diclofenac
Reporting group description:	
Over-encapsulated diclofenac sodium sustained-release (62.5 mg)/immediate-release (12.5 mg) tablets.	
Reporting group title	Lidocaine 5% medicated plaster
Reporting group description:	
Versatis® (lidocaine 5% medicated plaster, containing 700 mg lidocaine)	
Subject analysis set title	Placebo FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	GRT7019 FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	Diclofenac FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	
Subject analysis set title	Lidocaine 5% medicated plaster FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain.	

Primary: Change from baseline to week 4 of the double-blind treatment period in the weekly average pain intensity

End point title	Change from baseline to week 4 of the double-blind treatment period in the weekly average pain intensity
End point description:	
The primary endpoint was the change from baseline to Week 4 of the double-blind Treatment Period in the weekly average pain intensity. The baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the morning value of Day 1). Pain intensity was recorded twice daily (morning and evening) using an 11-point Numeric Rating Scale (NRS) with a half-day recall period (where 0 = no pain and 10 = Pain as bad as you can imagine). The weekly average pain was defined as the average of the non-missing weekly average morning and weekly average evening pain intensity assessments per trial week.	
End point type	Primary
End point timeframe:	
Baseline to Week 4 of the double-blind Treatment Period. Subjects used their eDiary to record their current pain intensity between 06:00 h and 09:00 h in the morning and once between 19:00 h and 22:00 h in the evening.	

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40[1]	41[2]	39[3]	41[4]
Units: units on a scale				
least squares mean (standard error)	-2.03 (± 0.27)	-1.83 (± 0.27)	-2.16 (± 0.26)	-1.44 (± 0.27)

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

[3] - Full Analysis Set

[4] - Full Analysis Set

Statistical analyses

Statistical analysis title	GRT7019 versus placebo

Statistical analysis description:

MMRM with fixed effects of pooled sites, treatment, time (in weeks), treatment-by-time interaction, positive expectancy score (of SETS questionnaire), and baseline intensity score. An unstructured covariance matrix is used to model the covariance structure, while denominator degrees of freedom are estimated using the Kenward-Roger approximation. The analysis was performed based on all post-baseline weekly pain intensities using only the observed cases without imputation of missing values.

Comparison groups	GRT7019 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	
Method	MMRM
Parameter estimate	MMRM
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.36

Secondary: Change from baseline to Week 4 of the double-blind Treatment Period in the weekly current morning pain intensity

End point title	Change from baseline to Week 4 of the double-blind Treatment Period in the weekly current morning pain intensity

End point description:

The average morning pain intensity is the mean of the morning pain intensities assessed once daily in the morning using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine) and asking the subject to "Please indicate how much osteoarthritis knee pain you have right now by selecting one number". A negative change indicates that there was a decrease in pain. If there were 4 or more missing morning pain intensity assessments in a week, the value for the weekly average morning pain intensity was set to missing.

End point type	Secondary

End point timeframe:

Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the morning pain intensity of Day -3 up to the morning value of Day 1), the change was up to 31 days after the start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[5]	45[6]	47[7]	45[8]
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to Week 1	-1.4 (± 1.2)	-1.1 (± 1.2)	-1.5 (± 1.4)	-1.2 (± 1.4)
Change from baseline to Week 2	-1.9 (± 1.5)	-1.7 (± 1.7)	-2.0 (± 1.8)	-1.6 (± 1.6)
Change from baseline to Week 3	-2.1 (± 1.6)	-1.9 (± 1.8)	-2.3 (± 1.8)	-1.6 (± 1.5)
Change from baseline to Week 4	-2.2 (± 1.6)	-2.0 (± 1.7)	-2.2 (± 2.0)	-1.7 (± 1.5)

Notes:

[5] - Full Analysis Set
(N = 45 at Week 1)
(N = 44 at Week 2)
(N = 41 at Week 3)
(N = 40 at Week 4)
[6] - Full Analysis Set
(N = 45 at Week 1)
(N = 45 at Week 2)
(N = 42 at Week 3)
(N = 41 at Week 4)
[7] - Full Analysis Set
(N = 47 at Week 1)
(N = 46 at Week 2)
(N = 41 at Week 3)
(N = 39 at Week 4)
[8] - Full Analysis Set
(N = 45 at Week 1)
(N = 45 at Week 2)
(N = 44 at Week 3)
(N = 42 at Week 4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 4 of the double-blind Treatment Period in the weekly current evening pain intensity

End point title	Change from baseline to Week 4 of the double-blind Treatment Period in the weekly current evening pain intensity

End point description:

The average evening pain intensity is the mean of the evening pain intensities assessed once daily in the evening using an 11-point NRS (where 0 = no pain and 10 = pain as bad as you can imagine) and asking the subject to "Please indicate how much osteoarthritis knee pain you have right now by selecting one number." A negative change indicates that there was a decrease in pain. If there were 4 or more missing evening pain intensity assessments in a week, the value for the weekly average evening pain intensity was set to missing.

End point type	Secondary

End point timeframe:

Baseline pain intensity was calculated as the average of the 6 half-day pain intensities prior to first IMP (starting with the evening pain intensity of Day -3 up to the evening value of Day 1), the change was up to 31 days after the start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[9]	45[10]	47[11]	45[12]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to Week 1	-1.5 (± 1.3)	-0.8 (± 1.4)	-1.6 (± 1.3)	-0.9 (± 1.5)
Change from baseline to Week 2	-2.0 (± 1.4)	-1.5 (± 1.6)	-2.2 (± 1.7)	-1.5 (± 1.7)
Change from baseline to Week 3	-2.2 (± 1.6)	-1.8 (± 1.7)	-2.4 (± 1.8)	-1.5 (± 1.7)
Change from baseline to Week 4	-2.2 (± 1.7)	-1.9 (± 1.6)	-2.5 (± 2.0)	-1.6 (± 1.9)

Notes:

[9] - Full Analysis Set
(N = 45 at Week 1)
(N = 46 at Week 2)
(N = 43 at Week 3)
(N = 43 at Week 4)

[10] - Full Analysis Set
(N = 45 at Week 1)
(N = 45 at Week 2)
(N = 42 at Week 3)
(N = 41 at Week 4)

[11] - Full Analysis Set
(N = 47 at Week 1)
(N = 46 at Week 2)
(N = 43 at Week 3)
(N = 40 at Week 4)

[12] - Full Analysis Set
(N = 44 at Week 1)
(N = 45 at Week 2)
(N = 44 at Week 3)
(N = 42 at Week 4)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of responder rate

End point title	Assessment of responder rate

End point description:

A subject is listed as responder in the responder status if both sub-criteria ("At least 30% pain reduction at Week 4 on an 11-point NRS" and "Rescue medication intake at most 500 mg") are fulfilled.

End point type	Secondary

End point timeframe:

From first dose of investigational medicinal product (IMP) to Week 4 (End of the double-blind Treatment Period).

End point values	Placebo FAS	GRT7019 FAS	Diclofenac FAS	Lidocaine 5% medicated plaster FAS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46[13]	45[14]	47[15]	45[16]
Units: subjects				
Responder	19	19	23	16
Non responder	27	26	24	29
At least 30% pain reduction at Week 4	20	21	24	16
Rescue medication intake at most 500mg	39	36	39	41

Notes:

[13] - Full Analysis Set

[14] - Full Analysis Set

[15] - Full Analysis Set

[16] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pain intensity after physical exercise

End point title	Change from baseline in pain intensity after physical exercise

End point description:

Subjects were asked at the investigational site to walk a stair for 1 minute (Andersson et al. 2010). Pain was recorded on an 11-point Numeric Rating Scale (where 0 = no pain to 10 = pain as bad as you can imagine) directly afterwards by asking the question "Please indicate how much osteoarthritis knee pain you have right now by selecting one number". A negative change in pain intensity score indicates that there has been a decrease in pain from baseline.

End point type	Secondary

End point timeframe:

At Final Visit 29 days after starting treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44[17]	43[18]	42[19]	45[20]
Units: units of a scale				
arithmetic mean (standard deviation)	-2.0 (± 2.1)	-2.2 (± 1.9)	-2.2 (± 2.2)	-1.5 (± 2.3)

Notes:

[17] - Full Analysis Set

[18] - Full Analysis Set

[19] - Full Analysis Set

[20] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Average daily rescue medication intake during Week 4 of the double-blind Treatment Period

End point title	Average daily rescue medication intake during Week 4 of the double-blind Treatment Period

End point description:

The average daily rescue medication intake was calculated from the information captured in the eDiary reported in Week 4. In case of missing diary information, a day was imputed with 500 mg paracetamol intake.

End point type	Secondary

End point timeframe:

Final Visit 29 days after start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[21]	42[22]	42[23]	44[24]
Units: milligram(s)/24 hours				
arithmetic mean (standard deviation)	150.5 (± 368.9)	177.4 (± 359.0)	101.2 (± 301.0)	119.3 (± 333.6)

Notes:

[21] - Full Analysis Set

[22] - Full Analysis Set

[23] - Full Analysis Set

[24] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Western Ontario McMaster Score

End point title	Changes from baseline in Western Ontario McMaster Score

End point description:

The WOMAC is a valid, reliable, and responsive measure of outcome in knee OA (Roos et al. 1999). The WOMAC version used was the WOMAC™ LK3.1, 5-point Likert format. The WOMAC was chosen as a complementary assessment of efficacy. The scores of the 3 subscales pain, stiffness, physical function and the WOMAC index score were calculated. Each of the 5 response categories was assigned a numerical value (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme). Each WOMAC subscale score was calculated by a simple summation of the assigned values scored on the items. The WOMAC index score was calculated by summating the scores for the 3 subscales (McConnel et al. 2001). A negative value indicates that there has been an improvement since baseline.

End point type	Secondary

End point timeframe:

Final Visit 29 days after the start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44[25]	43[26]	43[27]	45[28]
Units: units on a scale				
arithmetic mean (standard deviation)				
Change in WOMAC Index Score	-17.8 (± 15.7)	-13.9 (± 13.1)	-20.3 (± 15.1)	-15.9 (± 15.7)
Change in WOMAC Subscale Pain	-4.1 (± 3.7)	-3.7 (± 3.2)	-4.6 (± 3.5)	-3.6 (± 3.3)
Change in WOMAC Subscale Stiffness	-1.5 (± 1.7)	-1.0 (± 1.6)	-1.7 (± 1.3)	-1.2 (± 1.6)
Change in WOMAXC Subscale Physical Function	-12.2 (± 11.5)	-9.2 (± 9.8)	-13.9 (± 11.5)	-11.0 (± 11.9)

Notes:

[25] - Full Analysis Set

[26] - Full Analysis Set

[27] - Full Analysis Set

[28] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC)

End point title	Patient Global Impression of Change (PGIC)

End point description:

Patient Global Impression of Change used a 7-point scale at Final Visit. The subject was asked to respond by indicating which category fitted best to the question: "Since the start of the study, my overall status is":
“Very much improved”,
“Much improved”,
“Minimally improved",
”No change” ,
“Minimally worse”,
“Much worse”, or
“Very much worse”.

End point type	Secondary

End point timeframe:

Final Visit 29 Days after starting treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[29]	45[30]	47[31]	45[32]
Units: subjects				
Very much improved	2	3	9	5
Much improved	13	12	17	12
Minimally improved	18	22	10	14
No change	9	6	5	11
Minimally worse	1	0	1	3
Much worse	1	0	0	0
Very much worse	0	0	0	0
Missing	2	2	5	0

Notes:

[29] - Full Analysis Set

[30] - Full Analysis Set

[31] - Full Analysis Set

[32] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician’s Global Impression of Change (CGIC)

End point title	Clinician’s Global Impression of Change (CGIC)

End point description:

The Clinician's Global Impression of Change used a 7-point scale at Final Visit. The clinician was asked to respond by indicating which category fitted best to the question: "Compared with the patient’s condition at Baseline, how has it changed?":
“Very much improved”,
“Much improved”,
“Minimally improved",
”No change” ,
“Minimally worse”,
“Much worse”, or
“Very much worse”.

End point type	Secondary

End point timeframe:

Final Visit 29 days after start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[33]	45[34]	47[35]	45[36]
Units: subjects				
Very much improved	2	3	9	1
Much improved	16	15	19	16
Minimally improved	14	16	9	13
No change	9	9	6	13
Minimally worse	2	0	0	2
Much worse	1	0	0	0
Very much worse	0	0	0	0
Missing	2	2	4	0

Notes:

[33] - Full Analysis Set

[34] - Full Analysis Set

[35] - Full Analysis Set

[36] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment emergent adverse events

End point title	Incidence of treatment emergent adverse events

End point description:

The number of subjects were categorized by the number of Treatment Emergent Adverse Events (none, one, two, three, four, five or more than 5 TEAEs).

End point type	Secondary

End point timeframe:

Final Follow-up Visit 31 days after start of treatment.

End point values	Placebo	GRT7019	Diclofenac	Lidocaine 5% medicated plaster
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[37]	46[38]	48[39]	45[40]
Units: subjects				
No TEAEs	30	34	27	29
One TEAE	10	8	15	13
Two TEAEs	6	3	6	3
Three TEAEs	0	1	0	0
Four TEAEs	0	0	0	0
Five TEAEs	0	0	0	0
More than 5 TEAEs	0	0	0	0

Notes:

[37] - Safety Set

[38] - Safety Set

[39] - Safety Set

[40] - Safety 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 topical application or oral intake of investigational medicinal product (IMP) up to and including Visit 7 (Follow-up visit, i.e. scheduled for Day 31).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo patches (matching GRT7019 and lidocaine 5% medicated plasters) and placebo capsules (matching over-encapsulated diclofenac sodium tablets)

Reporting group title	GRT7019

Reporting group description:

A fixed-dose combination patch containing 5% lidocaine (700 mg) and 1.3% diclofenac epolamine (182 mg)

Reporting group title	Diclofenac

Reporting group description:

Over-encapsulated diclofenac sodium sustained-release (62.5 mg)/immediate-release (12.5 mg) tablets

Reporting group title	Lidocaine 5% medicated plaster

Reporting group description:

Versatis® (lidocaine 5% medicated plaster, containing 700 mg lidocaine)

Serious adverse events	Placebo	GRT7019	Diclofenac
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	1 / 46 (2.17%)	0 / 48 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lidocaine 5% medicated plaster		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	GRT7019	Diclofenac
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 46 (32.61%)	11 / 46 (23.91%)	21 / 48 (43.75%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Application site haematoma			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Application site haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0

Application site pruritus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Application site reaction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Application site warmth			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Catarrh			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatine increased			

subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	2 / 48 (4.17%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	3 / 46 (6.52%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	3	0	0
Ligament sprain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Tendon rupture			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 46 (2.17%)	1 / 46 (2.17%)	1 / 48 (2.08%)
occurrences (all)	1	1	1
Paraesthesia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0

Abdominal pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
Abdominal pain upper			
subjects affected / exposed	2 / 46 (4.35%)	2 / 46 (4.35%)	1 / 48 (2.08%)
occurrences (all)	2	2	1
Diarrhoea			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
Dyspepsia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Faeces soft			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dandruff			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Erythema			

subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	5 / 48 (10.42%)
occurrences (all)	1	0	5
Bronchitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Gastroenteritis viral			

subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Lidocaine 5% medicated plaster		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 45 (35.56%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Application site haematoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Application site haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Application site pruritus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Application site reaction			

subjects affected / exposed occurrences (all) Application site warmth subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0		
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Catarrh subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1		
Investigations Blood creatine increased subjects affected / exposed occurrences (all) Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1		

Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Tendon rupture			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Faeces soft			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dandruff			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Petechiae			

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Influenza			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported