



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 McMaster 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 standard deviation | 61.2 ± 8.0 | 63.3 ± 7.5 | 61.0 ± 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 standard deviation | 170.7 ± 8.9 | 168.0 ± 9.6 | 167.3 ± 8.1 |
| Weight Units: kilogram(s) arithmetic mean standard deviation | 83.1 ± 13.9 | 83.4 ± 13.5 | 83.2 ± 12.4 |
| Body Mass Index Units: kilogram(s)/square meter arithmetic mean standard deviation | 28.4 ± 3.6 | 29.5 ± 3.5 | 29.8 ± 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 standard deviation | 50.9 ± 11.3 | 43.5 ± 12.5 | 48.7 ± 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 standard deviation | 5.76 ± 0.93 | 5.59 ± 0.90 | 5.55 ± 0.78 |
| History of osteoarthritis | | | |
| Answer to the question: "When were you diagnosed with OA of the knee?" | | | |
| Units: years arithmetic mean standard deviation | NA ± | NA ± | NA ± |
| 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 McMaster 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 | \pm | | |

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 summing 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 occurring 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 occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Application site reaction subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 48 (0.00%) 0 |
| Application site warmth subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 48 (0.00%) 0 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Immune system disorders Food allergy subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Catarrh subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 48 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 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 occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 2 / 48 (4.17%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 2 / 46 (4.35%) 2 | 1 / 48 (2.08%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 2 / 48 (4.17%) 2 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Faeces soft subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Gastrointestinal pain subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Haematochezia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 48 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 48 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Skin and subcutaneous tissue disorders Dandruff subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 46 (0.00%) 0 | 0 / 48 (0.00%) 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 | | | |

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

| | | | |
|--|----------------|--|--|
| 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