



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Femoral Nerve Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005179-25 |
| Trial protocol | BE DK |
| Global end of trial date | 30 June 2017 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 10 April 2021 |
| First version publication date | 10 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 402-C-326 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02713178 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pacira Pharmaceuticals |
| Sponsor organisation address | 5 Sylvan Way, Parsippany, United States, 07054 |
| Public contact | Pacira Medical Information, Pacira Pharmaceuticals, Inc., +1 855-793-9727 , medinfo@pacira.com |
| Scientific contact | Pacira Medical Information, Pacira Pharmaceuticals, Inc., +1 855-793-9727 , medinfo@pacira.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 | 30 June 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection femoral nerve block with EXPAREL in subjects undergoing primary unilateral total knee arthroplasty (TKA).

Protection of trial subjects:

Initially, unblinded review of the data and a relative risk analysis were to be conducted if any of the following, based on the incidence rate, were identified during blinded data review:

- Severe or serious AE of special interest (AESI), including cardiac AESI and neurologic AESI exceeding 5% and in at least 5 subjects
- Severe dizziness exceeding 10% or in at least 5 subjects
- Severe AEs or serious AEs (SAEs), regardless of relationship to study drug, exceeding 20% or in at least 10 subjects

If the risk relative to placebo was greater than 2, the study was to be either permanently stopped or the study eligibility criteria were to be revised to exclude subjects who were at a higher risk for a particular AE.

After review of the Study Stopping Rules with the FDA (05 January 2017), these were changed as follows:

- Incidence rate of severe or serious AESIs as defined by the protocol including cardiac AESIs and neurologic AESIs exceeding 5% or in at least 5 subjects
- Incidence rate of severe dizziness exceeding 10% or in at least 5 subjects
- Incidence rate of severe or SAEs regardless of relationship to study drug exceeding 20% or in at least 10 subjects

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 116 |
| Country: Number of subjects enrolled | Belgium: 109 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Worldwide total number of subjects | 230 |
| EEA total number of subjects | 114 |

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) | 100 |
| From 65 to 84 years | 128 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between June 3, 2016 and June 30, 2017 at 13 sites in the US and Europe

Pre-assignment

Screening details:

Participants were recruited between June 3, 2016 and June 30, 2017 at 13 sites in the US and Europe

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Only pharmacist and administrator were unblinded onsite. These personnel were not involved with study assessments. An unblinded CRA monitored the site data.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | EXPAREL 133 mg |

Arm description:

10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | EXPAREL |
| Investigational medicinal product code | |
| Other name | bupivacaine liposome injectable suspension |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Not mentioned |

Dosage and administration details:

10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|------------------|----------------|
| Arm title | EXPAREL 266 mg |
|------------------|----------------|

Arm description:

20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | EXPAREL |
| Investigational medicinal product code | |
| Other name | bupivacaine liposome injectable suspension |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Other use |

Dosage and administration details:

20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

20 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------|
| Investigational medicinal product name | Normal Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Other use |

Dosage and administration details:

20 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| Number of subjects in period 1 | EXPAREL 133 mg | EXPAREL 266 mg | Placebo |
|---------------------------------------|----------------|----------------|---------|
| Started | 75 | 76 | 79 |
| Completed | 75 | 73 | 74 |
| Not completed | 0 | 3 | 5 |
| Consent withdrawn by subject | - | 2 | 4 |
| Adverse event, non-fatal | - | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------------|
| Reporting group title | EXPAREL 133 mg |
| Reporting group description: 10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively | |
| Reporting group title | EXPAREL 266 mg |
| Reporting group description: 20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection femoral nerve block ≥ 1 h preoperatively | |
| Reporting group title | Placebo |
| Reporting group description: 20 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively | |

| Reporting group values | EXPAREL 133 mg | EXPAREL 266 mg | Placebo |
|---|----------------|----------------|------------|
| Number of subjects | 75 | 76 | 79 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 64.6 | 66.0 | 65.4 |
| standard deviation | ± 6.94 | ± 9.01 | ± 8.69 |
| Gender categorical Units: Subjects | | | |
| Female | 36 | 43 | 53 |
| Male | 39 | 33 | 26 |
| Race | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| Black or African American | 8 | 5 | 12 |
| Asian | 0 | 1 | 0 |
| White | 66 | 69 | 67 |
| Other | 1 | 0 | 0 |
| Unknown/not reported | 0 | 1 | 0 |
| Ethnicity Units: Subjects | | | |
| Hispanic of Latino | 2 | 2 | 2 |
| Not Hispanic or Latino | 73 | 74 | 75 |

| | | | |
|--|----|----|----|
| Unknown or not reported | 0 | 0 | 2 |
| American Society of Anesthesiologists classification (ASA) | | | |
| American Society of Anesthesiologists (ASA) classification was determined by physicians using the ASA Physical Status Classification System which assesses the patient's pre-anesthesia medical co-morbidities. ASA 1 patients would be considered a normal, healthy patient. ASA 2 is a patient with mild systemic disease (eg, smoker, well controlled diabetes or high blood pressure (HBP)). ASA 3 is a patient with severe systemic disease (eg poorly controlled diabetes or HBP). ASA 4 is a patient with severe systemic disease that is a constant threat to life (eg, recent myocardial infarction, stroke). | | | |
| Units: Subjects | | | |
| ASA 1 | 11 | 9 | 10 |
| ASA 2 | 41 | 41 | 46 |
| ASA 3 | 23 | 26 | 23 |
| ASA >/= 4 | 0 | 0 | 0 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 230 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 132 | | |
| Male | 98 | | |
| Race | | | |
| NIH/OMB | | | |
| Units: Subjects | | | |
| Black or African American | 25 | | |
| Asian | 1 | | |
| White | 202 | | |
| Other | 1 | | |
| Unknown/not reported | 1 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic of Latino | 6 | | |
| Not Hispanic or Latino | 222 | | |
| Unknown or not reported | 2 | | |
| American Society of Anesthesiologists classification (ASA) | | | |
| American Society of Anesthesiologists (ASA) classification was determined by physicians using the ASA | | | |

Physical Status Classification System which assesses the patient's pre-anesthesia medical co-morbidities. ASA 1 patients would be considered a normal, healthy patient. ASA 2 is a patient with mild systemic disease (eg, smoker, well controlled diabetes or high blood pressure (HBP)). ASA 3 is a patient with severe systemic disease (eg poorly controlled diabetes or HBP). ASA 4 is a patient with severe systemic disease that is a constant threat to life (eg, recent myocardial infarction, stroke).

| Units: Subjects | | | |
|-----------------|-----|--|--|
| ASA 1 | 30 | | |
| ASA 2 | 128 | | |
| ASA 3 | 72 | | |
| ASA >/= 4 | 0 | | |

End points

End points reporting groups

| | |
|--|----------------|
| Reporting group title | EXPAREL 133 mg |
| Reporting group description: 10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively | |
| Reporting group title | EXPAREL 266 mg |
| Reporting group description: 20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection femoral nerve block ≥ 1 h preoperatively | |
| Reporting group title | Placebo |
| Reporting group description: 20 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively | |

Primary: Measure title AUC of VAS pain intensity scores through 72 hours

| | |
|---|---|
| End point title | Measure title AUC of VAS pain intensity scores through 72 hours |
| End point description: AUC of VAS pain intensity scores through 72 hours. PAin intensity scores were measured on a 10-cm VAS (0=no pain and 10=worst possible pain). | |
| End point type | Primary |
| End point timeframe: 0-72 hours | |

| End point values | EXPAREL 133 mg | EXPAREL 266 mg | Placebo | |
|---|-------------------------|-------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 75 | 76 | 79 | |
| Units: AUC of pain scores on VAS scales | | | | |
| least squares mean (standard error) | 259.545 (\pm 19.011) | 250.998 (\pm 18.849) | 279.794 (\pm 18.493) | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | AUC VAS EXPAREL 133mg |
| Comparison groups | EXPAREL 133 mg v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4463 |
| Method | ANOVA |
| Parameter estimate | LSMD |
| Point estimate | -20.249 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -72.361 |
| upper limit | 31.864 |

| | |
|---|--------------------------|
| Statistical analysis title | AUC VAS EXPAREL 266 mg |
| Comparison groups | EXPAREL 266 mg v Placebo |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2749 |
| Method | ANOVA |
| Parameter estimate | LSMD |
| Point estimate | -28.796 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -80.483 |
| upper limit | 22.892 |

| | |
|--|--|
| Secondary: Total postsurgical opioid consumption through 72 hours | |
| End point title | Total postsurgical opioid consumption through 72 hours |
| End point description: Total postsurgical opioid consumption (converted to IV morphine equivalents) through 72 hours. | |
| End point type | Secondary |
| End point timeframe: 0-72 hours | |

| | | | | |
|-------------------------------------|------------------|------------------|------------------|--|
| End point values | EXPAREL 133 mg | EXPAREL 266 mg | Placebo | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 75 | 76 | 79 | |
| Units: mg | | | | |
| least squares mean (standard error) | 69.466 (± 4.403) | 74.393 (± 4.669) | 81.469 (± 5.006) | |

| | |
|-----------------------------------|--|
| Statistical analyses | |
| Statistical analysis title | Total postsurgical opioid consumption EXPAREL 133m |
| Comparison groups | EXPAREL 133 mg v Placebo |

| | |
|---|---------------------|
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.314 |
| Method | ANOVA |
| Parameter estimate | LSM treatment ratio |
| Point estimate | 0.906 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.748 |
| upper limit | 1.098 |

| | |
|---|--|
| Statistical analysis title | Total postsurgical opioid consumption EXPAREL 266m |
| Comparison groups | EXPAREL 266 mg v Placebo |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9369 |
| Method | ANOVA |
| Parameter estimate | LSM treatment ratio |
| Point estimate | 1.008 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.833 |
| upper limit | 1.218 |

Secondary: Percentage of opioid free participants EXPAREL 133mg

| | |
|---|--|
| End point title | Percentage of opioid free participants EXPAREL 133mg |
| End point description: | |
| Percentage of participants who did not receive opioid medication through 72 hours | |
| End point type | Secondary |
| End point timeframe: | |
| 0-72 hours | |

| End point values | EXPAREL 133 mg | EXPAREL 266 mg | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 75 | 76 | 79 | |
| Units: participants | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to day 29 postsurgery

Adverse event reporting additional description:

adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug-related. An AE could therefore have been any unfavorable and unintended sign (eg, abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug without judgment about causality

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | EXPAREL 133 mg |
|-----------------------|----------------|

Reporting group description:

10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|-----------------------|----------------|
| Reporting group title | EXPAREL 266 mg |
|-----------------------|----------------|

Reporting group description:

20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection femoral nerve block ≥ 1 h preoperatively

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

20 mL normal saline as single-injection femoral nerve block ≥ 1 h preoperatively

| Serious adverse events | EXPAREL 133 mg | EXPAREL 266 mg | Placebo |
|---|----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 75 (6.67%) | 8 / 76 (10.53%) | 6 / 79 (7.59%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| postprocedural hematoma | | | |
| subjects affected / exposed | 3 / 75 (4.00%) | 1 / 76 (1.32%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| postprocedural swelling | | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 76 (0.00%) | 0 / 79 (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 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 1 / 76 (1.32%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 1 / 76 (1.32%) | 0 / 79 (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 |
| Nervous system disorders | | | |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 2 / 76 (2.63%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| transient ischemic attack | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 1 / 76 (1.32%) | 0 / 79 (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 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 1 / 76 (1.32%) | 0 / 79 (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 |
| Reproductive system and breast disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 1 / 76 (1.32%) | 0 / 79 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory depression | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 76 (0.00%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| Non-serious adverse events | EXPAREL 133 mg | EXPAREL 266 mg | Placebo |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 73 / 75 (97.33%) | 74 / 76 (97.37%) | 76 / 79 (96.20%) |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 7 / 75 (9.33%) | 1 / 76 (1.32%) | 3 / 79 (3.80%) |
| occurrences (all) | 7 | 1 | 3 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 3 / 76 (3.95%) | 5 / 79 (6.33%) |
| occurrences (all) | 1 | 3 | 5 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 75 (5.33%) | 5 / 76 (6.58%) | 0 / 79 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 4 / 75 (5.33%) | 1 / 76 (1.32%) | 0 / 79 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 8 / 75 (10.67%) | 4 / 76 (5.26%) | 5 / 79 (6.33%) |
| occurrences (all) | 9 | 4 | 5 |
| Nervous system disorders | | | |
| Motor dysfunction | | | |
| subjects affected / exposed | 34 / 75 (45.33%) | 35 / 76 (46.05%) | 34 / 79 (43.04%) |
| occurrences (all) | 35 | 37 | 34 |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 75 (4.00%) | 2 / 76 (2.63%) | 6 / 79 (7.59%) |
| occurrences (all) | 3 | 2 | 6 |
| Sensory loss | | | |
| subjects affected / exposed | 2 / 75 (2.67%) | 6 / 76 (7.89%) | 1 / 79 (1.27%) |
| occurrences (all) | 2 | 6 | 1 |
| Headache | | | |
| subjects affected / exposed | 4 / 75 (5.33%) | 2 / 76 (2.63%) | 0 / 79 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 76 (0.00%) | 4 / 79 (5.06%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|--|------------------------|------------------------|------------------------|
| Dizziness subjects affected / exposed occurrences (all) | 3 / 75 (4.00%) 5 | 7 / 76 (9.21%) 7 | 5 / 79 (6.33%) 7 |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 75 (1.33%) 1 | 2 / 76 (2.63%) 2 | 4 / 79 (5.06%) 5 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 75 (1.33%) 1 | 6 / 76 (7.89%) 6 | 5 / 79 (6.33%) 5 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 23 / 75 (30.67%) 23 | 18 / 76 (23.68%) 18 | 22 / 79 (27.85%) 22 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 75 (0.00%) 0 | 7 / 76 (9.21%) 7 | 3 / 79 (3.80%) 3 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 27 / 75 (36.00%) 28 | 34 / 76 (44.74%) 35 | 24 / 79 (30.38%) 26 |
| Constipation subjects affected / exposed occurrences (all) | 12 / 75 (16.00%) 12 | 16 / 76 (21.05%) 16 | 15 / 79 (18.99%) 15 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 75 (5.33%) 4 | 10 / 76 (13.16%) 10 | 9 / 79 (11.39%) 9 |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 75 (2.67%) 2 | 5 / 76 (6.58%) 5 | 2 / 79 (2.53%) 2 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 4 / 75 (5.33%) 4 | 8 / 76 (10.53%) 8 | 10 / 79 (12.66%) 10 |
| Psychiatric disorders | | | |

| | | | |
|---|--|---|--|
| Insomnia subjects affected / exposed occurrences (all) | 1 / 75 (1.33%) 1 | 1 / 76 (1.32%) 1 | 4 / 79 (5.06%) 4 |
| Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all) | 3 / 75 (4.00%) 3 | 10 / 76 (13.16%) 10 | 8 / 79 (10.13%) 8 |
| Musculoskeletal and connective tissue disorders Muscle twitching subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) | 5 / 75 (6.67%) 6 2 / 75 (2.67%) 2 | 7 / 76 (9.21%) 12 2 / 76 (2.63%) 2 | 4 / 79 (5.06%) 5 5 / 79 (6.33%) 5 |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 75 (6.67%) 5 | 5 / 76 (6.58%) 5 | 5 / 79 (6.33%) 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|-------------|
| 15 February 2016 | Amendment 1 |
| 28 September 2016 | Amendment 2 |
| 14 November 2016 | Amendment 3 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|------|
| none |
|------|

Notes: