Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Brachial Plexus Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Shoulder Arthroplasty or Rotator Cuff Repair

Summary

EudraCT number	2015-005228-24
Trial protocol	BE DK
Global end of trial date	07 July 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-327

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02713230
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pacira Pharmaceuticals, Inc.
Sponsor organisation address	5 Sylvan Way, Parsippany, United States, 07054
Public contact	Clinical Research Director, Pacira Pharmaceuticals, Inc., +1 855-793-9727 , medinfo@pacira.com
Scientific contact	Clinical Research Director, 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	07 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 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 brachial plexus block with EXPAREL in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.

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-Jan-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

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	Belgium: 19
Country: Number of subjects enrolled	Denmark: 21
Country: Number of subjects enrolled	United States: 115
Worldwide total number of subjects	155
EEA total number of subjects	40

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)	103
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between May 9, 2016 and July 7, 2017 at 16 sites in the US and Europe.

Pre-assignment

Screening details:

"Started" does not include one patient who was a screen failure, was not enrolled, and was randomized to placebo in error.

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	EXPAREL 133 mg

Arm description:

10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥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	Perineural use

Dosage and administration details:

EXPAREL 133 mg
10 mL EXPAREL (bupivacaine liposome injectable suspension) expanded with 10 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively

Arm title	EXPAREL 266 mg

Arm description:

20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively

Arm type	Experimental
Investigational medicinal product name	EXPAREL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Perineural use

Dosage and administration details:

20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively

Arm title	Placebo

Arm description:

20 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively

Arm type	Placebo

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

Dosage and administration details:

20 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively

Number of subjects in period 1	EXPAREL 133 mg	EXPAREL 266 mg	Placebo
Started	69	15	71
Completed	68	15	71
Not completed	1	0	0
Physician decision	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 brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	EXPAREL 266 mg
Reporting group description:	
20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	Placebo
Reporting group description:	
20 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	

Reporting group values	EXPAREL 133 mg	EXPAREL 266 mg	Placebo
Number of subjects	69	15	71
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			
Safety population included all participants who received study drug, with analysis by actual treatment received.			
Units: years arithmetic mean standard deviation	 60.6 ± 9.94	 61.4 ± 7.73	 58.5 ± 9.48
Gender categorical Units: Subjects			
Female	25	7	23
Male	44	8	48
Ethnicity Units: Subjects			
Hispanic or Latino	3	0	5
Not Hispanic or Latino	64	15	65
Unknown or Not Reported	2	0	1
Dominant hand Units: Subjects			
Left hand	10	1	10
Right hand	59	14	61
American Society of Anesthesiologists			

classification			
Measure Description: 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 i			
Units: Subjects			
ASA 1	15	1	14
ASA 2	36	9	37
ASA 3	18	5	20
ASA >/= 4	0	0	0
Nerve block type Units: Subjects			
Interscalene	67	15	70
Supraclavicular	2	0	1
Type of surgery Units: Subjects			
Rotator Cuff Surgery	50	7	55
Total Shoulder arthroplasty	19	8	16
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	13	4	15
White	53	11	54
More than one race	0	0	0
Unknown or not reported	2	0	2
Visual Analog Scale Pain Score			
Measure Description: Visual Analog Scale (VAS) is a pain scale. The VAS was presented as a straight 10 cm line, where 0 cm is no pain and 10 cm is the worst pain possible. Patients were asked, "How much pain are you experiencing right now? Please place a vertical mark on the line below to indicate the level of pain you are experiencing right now."			
Units: score on scale			
arithmetic mean	2.43	2.51	2.94
standard deviation	± 2.621	± 2.641	± 2.514

Reporting group values	Total		
Number of subjects	155		
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			
Safety population included all participants who received study drug, with analysis by actual treatment received.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	55		
Male	100		
Ethnicity			
Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	144		
Unknown or Not Reported	3		
Dominant hand			
Units: Subjects			
Left hand	21		
Right hand	134		
American Society of Anesthesiologists classification			
Measure Description: 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 i			
Units: Subjects			
ASA 1	30		
ASA 2	82		
ASA 3	43		
ASA >/= 4	0		
Nerve block type			
Units: Subjects			
Interscalene	152		
Supraclavicular	3		
Type of surgery			
Units: Subjects			
Rotator Cuff Surgery	112		
Total Shoulder arthroplasty	43		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	32		
White	118		
More than one race	0		
Unknown or not reported	4		
Visual Analog Scale Pain Score			
Measure Description: Visual Analog Scale (VAS) is a pain scale. The VAS was presented as a straight 10 cm line, where 0 cm is no pain and 10 cm is the worst pain possible. Patients were asked, "How much pain are you experiencing right now? Please place a vertical mark on the line below to indicate the level			

of pain you are experiencing right now."			
Units: score on scale arithmetic mean standard deviation	- -		

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 brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	EXPAREL 266 mg
Reporting group description:	
20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	Placebo
Reporting group description:	
20 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	

Primary: Area Under the Curve (AUC) of Visual Analog Scale (VAS) Pain Intensity Scores

End point title	Area Under the Curve (AUC) of Visual Analog Scale (VAS) Pain Intensity Scores[1]
End point description:	
AUC of VAS pain intensity scores through 48 hours, which represents total pain experienced through 48 hours. VAS is a pain scale. The VAS was presented as a straight 10 cm line, where 0 cm is no pain and 10 cm is the worst pain possible. Patients were asked, "How much pain are you experiencing right now? Please place a vertical mark on the line below to indicate the level of pain you are experiencing right now."	
End point type	Primary
End point timeframe:	
0-48 hours	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Under protocol amendment 2, the study arm 266 mg dose of EXPAREL was removed from randomization scheme and efficacy endpoints.	

End point values	EXPAREL 133 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: cm*hr				
least squares mean (standard error)	136.431 (± 12.090)	254.119 (± 11.768)		

Statistical analyses

Statistical analysis title	statistical analysis 1
Comparison groups	EXPAREL 133 mg v Placebo

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LSMD
Point estimate	-117.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	-150.896
upper limit	-84.48

Secondary: Total Postsurgical Opioid Consumption Through 48 Hours

End point title	Total Postsurgical Opioid Consumption Through 48 Hours[2]

End point description:

Total postsurgical opioid consumption (converted to IV morphine equivalents) through 48 hours

End point type	Secondary

End point timeframe:

0-48 hours

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Under protocol amendment 2, the study arm 266 mg dose of EXPAREL was removed from randomization scheme and efficacy endpoints.

End point values	EXPAREL 133 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: mg				
least squares mean (standard error)	25.007 (± 5.350)	109.739 (± 22.972)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	EXPAREL 133 mg v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LSM treatment ratio
Point estimate	0.228

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.126
upper limit	0.411

Secondary: Percentage of Opioid-free Participants Through 48 Hours

End point title	Percentage of Opioid-free Participants Through 48 Hours[3]

End point description:

Percentage of participants who did not receive opioid medication through 48 hours

End point type	Secondary

End point timeframe:

0-48 hours

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Under protocol amendment 2, the study arm 266 mg dose of EXPAREL was removed from randomization scheme and efficacy endpoints.

End point values	EXPAREL 133 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: participants	9	1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	EXPAREL 133 mg v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.2

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening to postsurgical day 29	
Adverse event reporting additional description:	
An 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 any judgment about ca	
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 brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	EXPAREL 266 mg
Reporting group description:	
20 mL EXPAREL (bupivacaine liposome injectable suspension) as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	
Reporting group title	Placebo
Reporting group description:	
20 mL normal saline as single-injection brachial plexus block (interscalene or supraclavicular) ≥1 h preoperatively	

Serious adverse events	EXPAREL 133 mg	EXPAREL 266 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 69 (2.90%)	1 / 15 (6.67%)	1 / 71 (1.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 15 (6.67%)	0 / 71 (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
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 15 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 15 (0.00%)	0 / 71 (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
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 69 (1.45%)	0 / 15 (0.00%)	0 / 71 (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	55 / 69 (79.71%)	11 / 15 (73.33%)	55 / 71 (77.46%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 69 (2.90%)	3 / 15 (20.00%)	6 / 71 (8.45%)
occurrences (all)	2	3	6
Hypotension			
subjects affected / exposed	1 / 69 (1.45%)	1 / 15 (6.67%)	2 / 71 (2.82%)
occurrences (all)	1	1	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 69 (1.45%)	1 / 15 (6.67%)	0 / 71 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 69 (2.90%)	1 / 15 (6.67%)	9 / 71 (12.68%)
occurrences (all)	2	1	10
Headache			
subjects affected / exposed	7 / 69 (10.14%)	1 / 15 (6.67%)	3 / 71 (4.23%)
occurrences (all)	7	1	3
Dysgeusia			
subjects affected / exposed	6 / 69 (8.70%)	0 / 15 (0.00%)	3 / 71 (4.23%)
occurrences (all)	6	0	3
Hypoaesthesia			

subjects affected / exposed	6 / 69 (8.70%)	0 / 15 (0.00%)	1 / 71 (1.41%)
occurrences (all)	7	0	1
Paraesthesia			
subjects affected / exposed	1 / 69 (1.45%)	1 / 15 (6.67%)	1 / 71 (1.41%)
occurrences (all)	1	1	1
Sensory loss			
subjects affected / exposed	2 / 69 (2.90%)	1 / 15 (6.67%)	0 / 71 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 69 (8.70%)	1 / 15 (6.67%)	3 / 71 (4.23%)
occurrences (all)	6	1	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	17 / 69 (24.64%)	3 / 15 (20.00%)	26 / 71 (36.62%)
occurrences (all)	19	3	27
Constipation			
subjects affected / exposed	6 / 69 (8.70%)	2 / 15 (13.33%)	9 / 71 (12.68%)
occurrences (all)	6	2	9
Vomiting			
subjects affected / exposed	4 / 69 (5.80%)	1 / 15 (6.67%)	7 / 71 (9.86%)
occurrences (all)	4	1	7
Dyspepsia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 15 (0.00%)	4 / 71 (5.63%)
occurrences (all)	1	0	4
Abdominal pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 15 (6.67%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 69 (4.35%)	1 / 15 (6.67%)	11 / 71 (15.49%)
occurrences (all)	3	1	11
Rash			
subjects affected / exposed	0 / 69 (0.00%)	1 / 15 (6.67%)	1 / 71 (1.41%)
occurrences (all)	0	1	1
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 69 (2.90%)	1 / 15 (6.67%)	0 / 71 (0.00%)
occurrences (all)	2	1	0
Anxiety			
subjects affected / exposed	1 / 69 (1.45%)	1 / 15 (6.67%)	0 / 71 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Muscle twitching			
subjects affected / exposed	5 / 69 (7.25%)	2 / 15 (13.33%)	8 / 71 (11.27%)
occurrences (all)	6	2	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2016	Amendment 1
14 November 2016	Amendment 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported