



## Clinical trial results:

### **A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy**

#### **Summary**

EudraCT number	2012-003275-19
Trial protocol	CZ PL BG
Global end of trial date	20 June 2013

#### **Results information**

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	402-C-322
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01802411
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Pacira Pharmaceuticals
Sponsor organisation address	5 Sylvan Way, Parsippany, United States, 07054
Public contact	Clinical Operations, Pacira Pharmaceuticals, Inc., +1 858-625-2424, medinfo@pacira.com
Scientific contact	Clinical Operations, Pacira Pharmaceuticals, Inc., +1 858-625-2424, jennifer.gordon@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	19 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 June 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of intercostal nerve block using liposome bupivacaine compared with placebo in subjects undergoing posterolateral thoracotomy.

Protection of trial subjects:

Post surgical rescue pain medication was provided as necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Czechia: 35
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Georgia: 27
Worldwide total number of subjects	185
EEA total number of subjects	153

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)	126
From 65 to 84 years	59



## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Before a subject underwent any study-specific screening procedures, the Investigator/designee explained the study purpose, procedures, expected effects and potential adverse reactions. A copy of the IRB- or IEC-approved ICF was provided to the subject, who was given sufficient time to ask questions and decide whether or not to participate.

### 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, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	EXPAREL 266 mg

Arm description:

Intercostal nerve block using single total administration of 20 mL EXPAREL (bupivacaine liposome injectable suspension) 266 mg (approximately 88 mg [6.6 mL] to each of three nerve segments)

Arm type	Active comparator
Investigational medicinal product name	EXPAREL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

Intercostal nerve block using single total administration of 20 mL EXPAREL (bupivacaine liposome injectable suspension) 266 mg (approximately 88 mg [6.6 mL] to each of three nerve segments)

<b>Arm title</b>	Placebo
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Arm description:

Intercostal nerve block using single total administration of 20 mL normal saline (6.6 mL to each of three nerve segments)

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Intercostal nerve block using single total administration of 20 mL normal saline (6.6 mL to each of three nerve segments)

<b>Number of subjects in period 1</b>	EXPAREL 266 mg	Placebo
Started	94	91
Completed	82	74
Not completed	12	17
Adverse event, serious fatal	2	1
Adverse event, non-fatal	2	6
Lack of efficacy	8	10

## Baseline characteristics

### Reporting groups

Reporting group title	EXPAREL 266 mg
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Reporting group description:

Intercostal nerve block using single total administration of 20 mL EXPAREL (bupivacaine liposome injectable suspension) 266 mg (approximately 88 mg [6.6 mL] to each of three nerve segments)

Reporting group title	Placebo
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Reporting group description:

Intercostal nerve block using single total administration of 20 mL normal saline (6.6 mL to each of three nerve segments)

Reporting group values	EXPAREL 266 mg	Placebo	Total
Number of subjects	94	91	185
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	57.9	58.5	
standard deviation	± 12.71	± 13.03	-
Gender categorical			
Units: Subjects			
Female	30	31	61
Male	64	60	124
Race			
Units: Subjects			
White	94	91	185
Not Recorded	0	0	0
Ethnic Group			
Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	90	88	178
Not Recorded	0	0	0
ASA Class			
American Society of Anesthesiologists			
Units: Subjects			
ASA 1	32	24	56
ASA 2	48	50	98
ASA 3	14	17	31

height (cm)			
Units: cm			
arithmetic mean	170.7	169.8	
standard deviation	± 8.87	± 8.22	-
weight (kg)			
Units: kg			
arithmetic mean	77.0	75.8	
standard deviation	± 15.0	± 12.96	-

## End points

### End points reporting groups

Reporting group title	EXPAREL 266 mg
Reporting group description:	Intercostal nerve block using single total administration of 20 mL EXPAREL (bupivacaine liposome injectable suspension) 266 mg (approximately 88 mg [6.6 mL] to each of three nerve segments)
Reporting group title	Placebo
Reporting group description:	Intercostal nerve block using single total administration of 20 mL normal saline (6.6 mL to each of three nerve segments)

### Primary: Area Under the Curve (AUC) of Pain Intensity at Rest Through 72 Hours

End point title	Area Under the Curve (AUC) of Pain Intensity at Rest Through 72 Hours
End point description:	AUC of pain intensity scores at rest through 72 hours postsurgery. Participants assumed a resting position that did not exacerbate his or her postsurgical pain. Pain intensity scores were measured at baseline and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours postsurgery, at first request for rescue pain medication, and on day 12 using the numeric rating scale at rest (NRS-R; 0=no pain and 10=worst possible pain).
End point type	Primary
End point timeframe:	0, 1, 2, 4, 8, 12, 36, 48, 60, and 72 hours post surgery

End point values	EXPAREL 266 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: score on a scale * hr				
least squares mean (standard error)	472.1 ( $\pm$ 37.19)	459.0 ( $\pm$ 36.57)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	EXPAREL 266 mg v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5598
Method	ANCOVA
Parameter estimate	LSMD
Point estimate	13.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31
upper limit	57

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### 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 (morphine equivalent) through 72 hours postsurgery
End point type	Secondary
End point timeframe:	0-72 hours post surgery

End point values	EXPAREL 266 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: mg morphine equivalent dose				
arithmetic mean (standard deviation)	70.88 (± 37.537)	71.38 (± 39.418)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From time of randomization through the day 30 follow-up contact

Adverse event reporting additional description:

The safety population included all participants who received study drug, with analysis based on actual treatment received. Treatment-emergent adverse events that were solicited from the neurological assessment or from the opioid-related AE questionnaire were included in this table.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	EXPAREL 266 mg
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Reporting group description:

Intercostal nerve block using single total administration of 20 mL EXPAREL (bupivacaine liposome injectable suspension) 266 mg (approximately 88 mg [6.6 mL] to each of three nerve segments)

Reporting group title	Placebo
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Reporting group description:

Intercostal nerve block using single total administration of 20 mL normal saline (6.6 mL to each of three nerve segments)

<b>Serious adverse events</b>	EXPAREL 266 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 94 (12.77%)	9 / 91 (9.89%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events	2	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Brain neoplasm			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
postprocedural hemorrhage			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart injury			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vascular disorders</b>			
Circulatory collapse			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
Cardiac arrest			
subjects affected / exposed	2 / 94 (2.13%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Myocardial infarction			

subjects affected / exposed	2 / 94 (2.13%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Atrial fibrillation</b>			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac failure acute</b>			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Nervous system disorders</b>			
<b>Cerebral haematoma</b>			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Coma uraemic</b>			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Pneumothorax</b>			
subjects affected / exposed	2 / 94 (2.13%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Acute respiratory failure</b>			
subjects affected / exposed	1 / 94 (1.06%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bronchial obstruction</b>			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
acute renal failure			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lobar pneumonia			

subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection Pseudomonal			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	EXPAREL 266 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 94 (67.02%)	54 / 91 (59.34%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 94 (8.51%)	5 / 91 (5.49%)	
occurrences (all)	9	5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 94 (2.13%)	7 / 91 (7.69%)	
occurrences (all)	2	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	7 / 94 (7.45%)	2 / 91 (2.20%)	
occurrences (all)	9	2	
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	15 / 94 (15.96%) 17	12 / 91 (13.19%) 12	
Fatigue subjects affected / exposed occurrences (all)	9 / 94 (9.57%) 9	4 / 91 (4.40%) 4	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	9 / 94 (9.57%) 9	7 / 91 (7.69%) 7	
Vomiting subjects affected / exposed occurrences (all)	9 / 94 (9.57%) 9	8 / 91 (8.79%) 9	
Skin and subcutaneous tissue disorders pruritus generalized subjects affected / exposed occurrences (all)	2 / 94 (2.13%) 2	5 / 91 (5.49%) 5	
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 7	4 / 91 (4.40%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Study drug delivery to intercostal nerve via instillation, not US-guided injection, likely prevented optimal placement/retention, as supported by pharmacokinetic data. Efficacy of study drug as regional nerve block could not be meaningfully evaluated

Notes: