Clinical trial results:
A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less
Than 17 Years

Summary

EudraCT number	2020-005985-33
Trial protocol	Outside EU/EEA
Global end of trial date	24 September 2019

Results information

Result version number	v1 (current)
This version publication date	28 June 2021
First version publication date	28 June 2021
Summary attachment (see zip file)	402-C-319 Clinical Study Report (CSR 402-C-319-final_13-may-2020.pdf)

Trial information

Trial identification

Sponsor protocol code	402-C-319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03682302
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	Jennifer Gordon, Pacira Pharmaceuticals, Inc., 1 9734514055, jennifer.gordon@pacira.com
Scientific contact	Jennifer Gordon, Pacira Pharmaceuticals, Inc., 1 9734514055, jennifer.gordon@pacira.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000877-PIP03-17
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 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the pharmacokinetics (PK) of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing surgery.

Protection of trial subjects:

Use of postsurgical pain medication in cases of insufficient analgesia was permitted according to each respective study site’s standard of care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2019
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: 95
Worldwide total number of subjects	95
EEA total number of subjects	0

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)	34
Adolescents (12-17 years)	61
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between 02 April 2019 and 24 September 2019 at 15 sites in the US (both Groups).

Pre-assignment

Screening details:

Subjects were screened within 30 days prior to study drug administration. During the screening visit, subjects were assessed for past or present neurologic, cardiac, and general medical conditions that, in the opinion of the investigator, would preclude them from study participation.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

open-label

Arms

Are arms mutually exclusive?	Yes
Arm title	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL

Arm description:

Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.

Arm type	Experimental
Investigational medicinal product name	EXPAREL
Investigational medicinal product code	
Other name	Liposomal bupivacaine, bupivacaine liposome injectable suspension
Pharmaceutical forms	Suspension for injection
Routes of administration	Infiltration

Dosage and administration details:

EXPAREL 4mg/kg (Maximum 266mg) single dose intraoperatively at the end of surgery via local infiltration

Arm title	G1: 12-<17 years, undergoing spine surgery, bupivacaine

Arm description:

Single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.

Arm type	Active comparator
Investigational medicinal product name	0.5% bupivacaine HCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infiltration

Dosage and administration details:

Single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.

Arm title	G2: 6-<12 years undergoing spine surgery, EXPAREL

Arm description:

Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.

Arm type	Experimental
Investigational medicinal product name	EXPAREL
Investigational medicinal product code	
Other name	Liposomal bupivacaine, bupivacaine liposome injectable suspension
Pharmaceutical forms	Suspension for injection
Routes of administration	Infiltration

Dosage and administration details:

Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.

Arm title	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL

Arm description:

Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of cardiac surgery.

Arm type	Experimental
Investigational medicinal product name	EXPAREL
Investigational medicinal product code	
Other name	Liposomal bupivacaine, bupivacaine liposome injectable suspension
Pharmaceutical forms	Suspension for injection
Routes of administration	Infiltration

Dosage and administration details:

Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.

Number of subjects in period 1	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL
Started	31	30	5
Completed	30	28	5
Not completed	1	2	0
Lost to follow-up	1	2	-

Number of subjects in period 1	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Started	29
Completed	28
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G1: 12-<17 years, undergoing spine surgery, bupivacaine
Reporting group description:	
Single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6-<12 years undergoing spine surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of cardiac surgery.	

Reporting group values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL
Number of subjects	31	30	5
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			
age in years			
Units: years			
arithmetic mean	13.8	13.9	10
standard deviation	± 1.33	± 1.33	± 1.73
Gender categorical			
Units: Subjects			
Female	28	22	2
Male	3	8	3
Ethnicity			
NIH/OMB			
Units: Subjects			
Hispanic or Latino	10	7	0
Not Hispanic or Latino	19	23	5

Unknown or Not Reported	2	0	0
Race			
NIH/OMB			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	3	1
White	21	26	4
More than one race	1	1	0
Unknown or Not Reported	2	0	0
American Society of Anesthesiologists classification			
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	14	13	1
ASA 2	16	13	2
ASA 3	1	4	2

Reporting group values	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL	Total	
Number of subjects	29	95	
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			
age in years			
Units: years			
arithmetic mean	8.7		
standard deviation	± 1.77	-	
Gender categorical			
Units: Subjects			
Female	14	66	
Male	15	29	
Ethnicity			
NIH/OMB			
Units: Subjects			
Hispanic or Latino	9	26	

Not Hispanic or Latino	20	67	
Unknown or Not Reported	0	2	
Race			
NIH/OMB			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	2	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	2	11	
White	26	77	
More than one race	0	2	
Unknown or Not Reported	0	2	
American Society of Anesthesiologists classification			
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	0	28	
ASA 2	2	33	
ASA 3	27	34	

End points

End points reporting groups

Reporting group title	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G1: 12-<17 years, undergoing spine surgery, bupivacaine
Reporting group description:	
Single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6-<12 years undergoing spine surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Reporting group description:	
Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of cardiac surgery.	

Primary: Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Infinity

End point title	Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Infinity[1]
End point description:	
The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.	
End point type	Primary
End point timeframe:	
15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h (cardiac surgery)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21
Units: ng*h/mL				
arithmetic mean (standard deviation)	14246.1 (± 9118.83)	5709.4 (± 3281.74)	11569.5 (± 7306.07)	26164.0 (± 28038.35)

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax)

End point title	Maximum Plasma Concentration (Cmax)[2]

End point description:

The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.

End point type	Primary

End point timeframe:

15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h(cardiac surgery)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21
Units: ng/mL				
arithmetic mean (standard deviation)	357.3 (± 125.31)	563.6 (± 320.93)	319.5 (± 164.76)	447.1 (± 243.41)

Statistical analyses

No statistical analyses for this end point

Primary: The Apparent Terminal Elimination Half-life (t1/2el)

End point title	The Apparent Terminal Elimination Half-life (t1/2el)[3]

End point description:

The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.

End point type	Primary

End point timeframe:

15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h (cardiac surgery)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21

Units: hours				
arithmetic mean (standard deviation)	26.8 (± 21.26)	8.4 (± 6.26)	13.4 (± 4.60)	24.9 (± 20.58)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Clearance (CL/F)

End point title	Apparent Clearance (CL/F)[4]

End point description:

The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.

End point type	Primary

End point timeframe:

15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h (cardiac surgery)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21
Units: liters/hour				
arithmetic mean (standard deviation)	17.5 (± 7.47)	20.5 (± 8.27)	14.5 (± 2.70)	7.4 (± 3.20)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution (Vd/F)

End point title	Apparent Volume of Distribution (Vd/F)[5]

End point description:

The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.

End point type	Primary

End point timeframe:

15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h (cardiac surgery)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21
Units: Liters				
arithmetic mean (standard deviation)	546.4 (± 269.42)	226.8 (± 110.63)	271.1 (± 43.58)	216.1 (± 83.77)

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Tlast

End point title	Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Tlast[6]

End point description:

The pharmacokinetic population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration, with analysis by actual treatment received.

End point type	Primary

End point timeframe:

15, 30, 45 min, 1-1.25h, 2-3h, 10-18h, 24-36h, 42-60h (spine surgery) or 15, 30, 45 min, 1-1.25, 15-25, 30-40, 45-55, 64-72h (cardiac surgery)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK analysis

End point values	G1: 12- < than 17 years, undergoing spine surgery, EXPAREL	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	2	21
Units: ng*h/mL				
arithmetic mean (standard deviation)	9042.5 (± 3762.82)	5232.9 (± 2538.37)	10249.6 (± 5956.56)	16776.4 (± 7935.80)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening through postsurgical Day 14	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	G1: 12-<17 years, undergoing spine surgery, bupivacaine
Reporting group description: Single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6-<12 years undergoing spine surgery, EXPAREL
Reporting group description: Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	
Reporting group title	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Reporting group description: Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of cardiac surgery.	
Reporting group title	Group 1: 12-< 17 years, undergoing spine surgery, EXPAREL
Reporting group description: Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery.	

Serious adverse events	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	2 / 29 (6.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
vomiting, persistent			
subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	1 / 29 (3.45%)
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			
Wound infection fungal			
subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 1: 12-< 17 years, undergoing spine surgery, EXPAREL		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
vomiting, persistent			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Wound infection fungal			
subjects affected / exposed	0 / 31 (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: 5 %

Non-serious adverse events	G1: 12-<17 years, undergoing spine surgery, bupivacaine	G2: 6-<12 years undergoing spine surgery, EXPAREL	G2: 6 - <12 years undergoing cardiac surgery, EXPAREL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 30 (73.33%)	5 / 5 (100.00%)	9 / 29 (31.03%)
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Delayed recovery from anesthesia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Seroma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 30 (23.33%)	2 / 5 (40.00%)	0 / 29 (0.00%)
occurrences (all)	7	2	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 30 (13.33%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Bradycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	2 / 30 (6.67%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Hypoaesthesia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Paranaesthesia			

subjects affected / exposed	2 / 30 (6.67%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision Blurred			
subjects affected / exposed	3 / 30 (10.00%)	3 / 5 (60.00%)	1 / 29 (3.45%)
occurrences (all)	3	3	1
Visual Impairment			
subjects affected / exposed	2 / 30 (6.67%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 30 (30.00%)	1 / 5 (20.00%)	4 / 29 (13.79%)
occurrences (all)	9	1	4
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	6 / 30 (20.00%)	1 / 5 (20.00%)	2 / 29 (6.90%)
occurrences (all)	6	1	2
Vomiting			
subjects affected / exposed	5 / 30 (16.67%)	1 / 5 (20.00%)	4 / 29 (13.79%)
occurrences (all)	5	1	4
Hypoaesthesia oral			
subjects affected / exposed	3 / 30 (10.00%)	3 / 5 (60.00%)	0 / 29 (0.00%)
occurrences (all)	3	3	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 30 (6.67%)	2 / 5 (40.00%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
pruritis generalized			
subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			

Incontinence			
subjects affected / exposed	0 / 30 (0.00%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscle twitching			
subjects affected / exposed	8 / 30 (26.67%)	1 / 5 (20.00%)	1 / 29 (3.45%)
occurrences (all)	10	1	1
Muscle spasms			
subjects affected / exposed	0 / 30 (0.00%)	1 / 5 (20.00%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	3 / 30 (10.00%)	0 / 5 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Group 1: 12-< 17 years, undergoing spine surgery, EXPAREL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 31 (61.29%)		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Delayed recovery from anesthesia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Seroma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Bradycardia			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Paranaesthesia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Eye disorders			
Vision Blurred			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Visual Impairment			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	10 / 31 (32.26%)		
occurrences (all)	10		
Vomiting			

subjects affected / exposed	9 / 31 (29.03%)		
occurrences (all)	9		
Hypoaesthesia oral			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
pruritis generalized			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Muscle twitching			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Muscular weakness			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		

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