Clinical trial results:
A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Local Administration of EXPAREL for Postsurgical Analgesia in Pediatric Subjects 12 to Less Than 17 Years of Age

Summary

EudraCT number	2023-000584-31
Trial protocol	Outside EU/EEA
Global end of trial date	12 February 2019

Results information

Result version number	v1 (current)
This version publication date	17 August 2023
First version publication date	17 August 2023

Trial information

Trial identification

Sponsor protocol code	402-C-120

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03485014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pacira Pharmaceuticals, Inc.
Sponsor organisation address	5 Sylvan Way, Parsippany/NJ, United States, 07054
Public contact	Medical Information, Pacira Pharmaceuticals, Inc., medinfo@pacira.com
Scientific contact	Medical Information, Pacira Pharmaceuticals, Inc., medinfo@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2019
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 pharmacokinetics of EXPAREL in pediatric subjects 12 to less than 17 years of age undergoing spinal surgery.

Protection of trial subjects:

The study was conducted in accordance with the clinical research guidelines established by the Food and Drug Administration (FDA) Title 21 Code of Federal Regulation (CFR), Parts 50 (including Subpart D regarding additional safeguards for children in clinical investigations), 54, 56, and 312. Any other requirements necessary for the protection of the human rights of the subject were also explained according to the current International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guideline and the Declaration of Helsinki. Subjects were allowed to be treated with prophylactic antibiotics according to surgeon´s preference, and with intraoperative opioids (other than ultra short-acting opioids [e.g., fentanyl, sufentanil, or remifentanil]), acetaminophen, ketorolac, or other nonsteroidal anti-inflammatory drugs in accordance with the study site´s standard of care.

Background therapy:

There were restrictions on the use of concomitant medications/therapies during the trial/surgery. The following medications/therapies were not permitted: use of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug prior to study drug administration, or planned administration of another investigational product or procedure during the subject´s participation in the study. In addition, no drugs were to be admixed with study drug (e.g., epinephrine, dexamethasone, clonidine). Lidocaine and other local anesthetics were not permitted intraoperatively.

Evidence for comparator:

This was a single treatment group where all eligible subjects were treated with the study drug: EXPAREL

Actual start date of recruitment	10 April 2018
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	United States: 15
Worldwide total number of subjects	15
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	15
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 subjects (12 to less than 17 years of age) were screened for eligibility in 1 trial site in the United States. All received the study drug and completed the study. No screening failures were reported.

Pre-assignment

Screening details:

15 male or female subjects, from 12 to less than 17 years of age on the day of surgery who had an American Society of Anesthesiologists Class of 1 to 3 were screened.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study where all eligible subjects were administered with EXPAREL

Arms

Arm title	EXPAREL

Arm description:

Eligible subjects received a single dose of EXPAREL (4 mg/kg) intraoperatively at the end of surgery via local infiltration into the surgical site. EXPARELwas administered prior to wound closure.

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

Dosage and administration details:

Single dose of EXPAREL (4 mg/kg) intraoperatively administered at the end of surgery via local infiltration into the surgical site. EXPAREL was administered prior to wound closure

Number of subjects in period 1	EXPAREL
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
Subjects receiving single injectable suspension of EXPAREL 4 mg/kg on Day 1 at the end of surgery into the surgical site.	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	15	15	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	14.7		
standard deviation	± 1.54	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	4	4	
Ethnicity Units: Subjects			
Not Hispanic or Latino	15	15	
Race Units: Subjects			
Black/African American	1	1	
White	11	11	
Other	3	3	
American Society of Anesthesiologists Classification Units: Subjects			
ASA 1	9	9	
ASA 2	4	4	
ASA 3	2	2	
Electrocardiogram Units: Subjects			
Normal	9	9	
Abnormal (not clinically significant)	6	6	

Height Units: centimetre arithmetic mean standard deviation	 162.86 ± 12.438	 -	
Weight Units: kilogram(s) arithmetic mean standard deviation	 55.06 ± 11.085	 -	
Body mass index Units: kilogram(s)/square metre arithmetic mean standard deviation	 20.53 ± 1.595	 -	

End points

End points reporting groups

Reporting group title	EXPAREL

Reporting group description:

Eligible subjects received a single dose of EXPAREL (4 mg/kg) intraoperatively at the end of surgery via local infiltration into the surgical site. EXPARELwas administered prior to wound closure.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set consisted of all subjects who underwent the planned surgery and received study drug

Subject analysis set title	Pharmacokinetics analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The pharmacokinetic analysis set included all subjects who received study drug and provided at least 1 quantifiable plasma concentration

Primary: AUC

End point title	AUC[1]

End point description:

Area under the plasma concentration-versus-time-curve
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subjects

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: microgram(s)/millilitre * h				
arithmetic mean (standard deviation)	10.1 (± 3.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Early Cmax

End point title	Early Cmax[2]

End point description:

Early maximum plasma concentration
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subjects

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	401 (± 128)			

Statistical analyses

No statistical analyses for this end point

Primary: Late Cmax

End point title	Late Cmax[3]

End point description:

Late maximum plasma concentration
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure,

inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subject

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	335 (± 106)			

Statistical analyses

No statistical analyses for this end point

Primary: T1/2el

End point title	T1/2el[4]

End point description:

The apparent terminal elimination half-life
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subjects

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: hour				
arithmetic mean (standard deviation)	3.57 (± 1.0)			

Statistical analyses

No statistical analyses for this end point

Primary: CL/F

End point title	CL/F[5]

End point description:

Apparent clearance
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subjects

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: litre(s)/hour				
arithmetic mean (standard deviation)	24.3 (± 5.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Vss

End point title	Vss[6]

End point description:

Apparent volume of distribution at steady-state
Per original protocol and protocol amendment 1, 5 blood samples were collected from each subject during scheduled time windows:
Group 1: blood samples were taken approximately 30 minutes, 190 minutes, 17.5 hours, 42.5 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
Group 2: blood samples were taken approximately 30 minutes, 210 minutes, 22.5 hours, 47.5 hours, and 72 to 96 hours after EXPAREL administration (3 subjects)
Group 3: blood samples were taken approximately 30 minutes, 230 minutes, 27.5 hours, 53 hours, and 72 to 96 hours after EXPAREL administration (2 subjects)
The population PK model estimated EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations following a predicted model.

End point type	Primary

End point timeframe:

Protocol Amendment 2: Eight blood samples were collected per subject as specific time windows (15 minutes, 30 minutes, 45 minutes, 1 to 1.25 hours, 2 to 3 hours, 10 to 18 hours, 24 to 36 hours, and 42 to 60 hours after EXPAREL administration) - 8 subject

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: Nonlinear mixed-effect modelling was used to analyse the sparse concentration-versus-time data. Because of different sampling times across sampling groups and small sample size for each sampling group, no non-compartmental PK parameters were derived and no summary was performed for the PK concentration by time point. The study was single arm and no statistical analyses were performed for this endpoint

End point values	Pharmacokinetics analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: litre(s)				
arithmetic mean (standard deviation)	116 (± 32.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the informed consent form (ICF) was signed/assent was obtained through end of the study (Day 30)

Adverse event reporting additional description:

Subjects were expected to volunteer information about adverse events that they experienced. In addition, the investigator or designee questioned the subject at each visit about adverse events and recorded these as well as other adverse events at the visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	EXPAREL

Reporting group description:

Eligible subjects received a single dose of Exparel (4 mg/kg) intraoperatively at the end of surgery via local infiltration into the surgical site. Exparel was administered prior to wound closure.

Serious adverse events	EXPAREL		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	EXPAREL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	14 / 15 (93.33%)		
occurrences (all)	15		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Gait disturbance			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	6		
Atelectasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	5 / 15 (33.33%) 5		
Tachycardia subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 8		
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Hypoaesthesia subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 4		
Burning sensation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	15 / 15 (100.00%) 15		
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Hypoacusis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Eye swelling subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Hypoaesthesia oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Lip swelling subjects affected / exposed occurrences (all)	 7 / 15 (46.67%) 7 2 / 15 (13.33%) 2 9 / 15 (60.00%) 9 8 / 15 (53.33%) 8 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 6 / 15 (40.00%) 7 1 / 15 (6.67%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2		
Musculoskeletal and connective tissue disorders Back pain			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Muscle twitching			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	10		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2018	The clinically relevant changes made under this protocol amendment are summarized below: - Specified that the baseline 12-lead electrocardiogram (ECG) may have been performed either at the screening visit or in the preoperative holding area on Day 1 prior to surgery - Added that a pregnancy test for female subjects of childbearing potential was to be conducted in the preoperative holding area according to the site´s study of care and a negative result for the pregnancy test must have been available prior to the start of surgery. - Removed local anesthetics (other than study drug) from the list of permitted intraoperative medications - Specified that a follow-up call was to occur on Day 7 and a follow-up physical examination, including examination of the surgical site, was to occur on Day 30. - Added that date and time of admission to the hospital were to be recorded on the day of surgery (Day 1) - Removed urine drug screen and blood alcohol test from screening procedures. Note: A total of 7 subjects of the 15 included were enrolled under amendment 1.
24 September 2018	The clinically relevant changes made under this protocol amendment are summarized below: - Added that the maximum single dose of EXPAREL in this study was to be 266 mg. - Changed the total number of pharmacokinetic (PK) samples from 5 to 8 and adjusted PK sample times and collection windows; PK blood draws were changes from starting at 30 minutes after the end of study drug administration and continuing at various timepoints through 96 hours to starting at 15 minutes after the end of study drug administration and continuing at various timepoints through 60 hours; removed different PK sampling groups, and therefore, also removed the need to randomize subjects to these PK sampling groups (Note: Footnote 7 of Protocol Table 1 specified measuring PK assessment from the start of study drug administration, and this instruction was followed by the investigator). - Added text describing the initial approval (2011) and amended indication approval (2018) of EXPAREL by the Food and Drug Administration (FDA). Note: A total of 8 subjects of the 15 included were enrolled under amendment 2

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 reported

Notes: