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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	402-C-326

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pacira Pharmaceuticals
Sponsor organisation address	5 Sylvan Way, Parsippany, United States, 07054
Public contact	Pacira Medical Information, Pacira Pharmaceuticals, Inc., +1 855-793-9727 , medinfo@pacira.com
Scientific contact	Pacira Medical Information, Pacira Pharmaceuticals, Inc., +1 855-793-9727 , medinfo@pacira.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Initially, unblinded review of the data and a relative risk analysis were to be conducted if any of the following, based on the incidence rate, were identified during blinded data review:
-Severe or serious AE of special interest (AESI), including cardiac
AESI and neurologic AESI exceeding 5% and in at least 5 subjects
-Severe dizziness exceeding 10% or in at least 5 subjects
-Severe AEs or serious AEs (SAEs), regardless of relationship to study drug, exceeding 20% or in at least 10 subjects
If the risk relative to placebo was greater than 2, the study was to be either permanently stopped or the study eligibility criteria were to be revised to exclude subjects who were at a higher risk for a particular AE.
After review of the Study Stopping Rules with the FDA (05 January 2017), these were changed as follows:
-Incidence rate of severe or serious AESIs as defined by the protocol including cardiac AESIs and neurologic AESIs exceeding 5% or in at least 5 subjects
-Incidence rate of severe dizziness exceeding 10% or in at least 5 subjects
Incidence rate of severe or SAEs regardless of relationship to study drug exceeding 20% or in at least 10 subjects

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	100
From 65 to 84 years	128
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	EXPAREL 133 mg

Arm description:

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

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

Dosage and administration details:

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

Arm title	EXPAREL 266 mg

Arm description:

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

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

Dosage and administration details:

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

Arm title	Placebo

Arm description:

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

Arm type	Placebo

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

Dosage and administration details:

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

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

Baseline characteristics

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

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

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

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

Physical Status Classification System which assesses the patient's pre-anesthesia medical co-morbidities. ASA 1 patients would be considered a normal, healthy patient. ASA 2 is a patient with mild systemic disease (eg, smoker, well controlled diabetes or high blood pressure (HBP)). ASA 3 is a patient with severe systemic disease (eg poorly controlled diabetes or HBP). ASA 4 is a patient with severe systemic disease that is a constant threat to life (eg, recent myocardial infarction, stroke).			
Units: Subjects			
ASA 1	30		
ASA 2	128		
ASA 3	72		
ASA >/= 4	0		

End points

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

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

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

Statistical analyses

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

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

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

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

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

Statistical analyses

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to day 29 postsurgery

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	EXPAREL 133 mg

Reporting group description:

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

Reporting group title	EXPAREL 266 mg

Reporting group description:

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

Reporting group title	Placebo

Reporting group description:

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

none

Notes: