Clinical trial results:
A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Comparative Systemic Bioavailability of a Single Administration of SKY0402 via Local Infiltration for Prolonged Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty

Summary

EudraCT number	2007-005115-26
Trial protocol	CZ AT DE DK
Global end of trial date	03 July 2008

Results information

Result version number	v1 (current)
This version publication date	24 June 2022
First version publication date	24 June 2022

Trial information

Trial identification

Sponsor protocol code	SKY0402-C-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00485693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pacira Pharmceuticals, Inc.
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, 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	25 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate four dose levels of SKY0402, compared with bupivacaine HCl, with respect to the extent and duration of the analgesic effect achieved by a single administration of the study drug via local infiltration.

Protection of trial subjects:

Prior to enrolling subjects into this study, the study site obtained the approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). This study was conducted in accordance with the clinical research guidelines established by Title 21 CFR, Parts 50, 54, 56, and 312 and the ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2007
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	Czechia: 41
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	138
EEA total number of subjects	41

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)	79
From 65 to 84 years	59

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion: Male or Female >/= 18 and </=75, scheduled to undergo primary unilateral TKA under general anesthesia, ASA class 1-3. Exclusion: use of long-acting opioid medication within 3 days, or any opioid medication within 24 hours, concurrent painful physical condition

Period 1

Period 1 title	Overall Study (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:

Blinded and unblinded Monitors were employed. Site specific blinding plans were created.

Arms

Are arms mutually exclusive?	Yes
Arm title	SKY0402 150mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SKY0402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infiltration

Dosage and administration details:

SKY0402 150mg/10mL + 0.9% NaCl 50mL for a total volume of 60mL

Arm title	SKY0402 300mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SKY0402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infiltration

Dosage and administration details:

SKY0402 300mg/20mL + 0.9% NaCl 40mL for a total volume of 60mL

Arm title	SKY0402 450 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SKY0402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infiltration

Dosage and administration details:

SKY0402 450mg/30mL + 0.9% NaCl 30mL for a total volume of 60mL

Arm title	SKY0402 600mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	SKY0402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infiltration

Dosage and administration details:

SKY0402 600mg/40mL + 0.9% NaCl 20mL for a total volume of 60mL

Arm title	0.25% Bupivacaine HCl 150mg
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	0.25% Bupivacaine HCl 150mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Infiltration

Dosage and administration details:

0.25% Bupivacaine HCl (Marcaine 0.25% with epinephrine 1:200,000) 150mg

Number of subjects in period 1	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg
Started	27	25	26
Completed	27	25	26
Not completed	0	0	0
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	SKY0402 600mg	0.25% Bupivacaine HCl 150mg
Started	25	35
Completed	24	32
Not completed	1	3
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	SKY0402 150mg
Reporting group description: -	
Reporting group title	SKY0402 300mg
Reporting group description: -	
Reporting group title	SKY0402 450 mg
Reporting group description: -	
Reporting group title	SKY0402 600mg
Reporting group description: -	
Reporting group title	0.25% Bupivacaine HCl 150mg
Reporting group description: -	

Reporting group values	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg
Number of subjects	27	25	26
Age categorical Units: Subjects			
Adults (18-64 years)	16	15	16
From 65-84 years	11	10	10
Not Recorded	0	0	0
Gender categorical Units: Subjects			
Female	14	12	15
Male	13	13	11
not recorded	0	0	0

Reporting group values	SKY0402 600mg	0.25% Bupivacaine HCl 150mg	Total
Number of subjects	25	35	138
Age categorical Units: Subjects			
Adults (18-64 years)	11	21	79
From 65-84 years	14	14	59
Not Recorded	0	0	0
Gender categorical Units: Subjects			
Female	20	24	85
Male	5	11	53
not recorded	0	0	0

End points

End points reporting groups

Reporting group title	SKY0402 150mg
Reporting group description: -	
Reporting group title	SKY0402 300mg
Reporting group description: -	
Reporting group title	SKY0402 450 mg
Reporting group description: -	
Reporting group title	SKY0402 600mg
Reporting group description: -	
Reporting group title	0.25% Bupivacaine HCl 150mg
Reporting group description: -	

Primary: Area under the curve (AUC) of the numeric rating scale (NRS) with activity (NRS-A) pain intensity scores through postoperative Day 4

End point title	Area under the curve (AUC) of the numeric rating scale (NRS) with activity (NRS-A) pain intensity scores through postoperative Day 4

End point description:

The subject's pain intensity was to be assessed with activity (NRS-A) after actively flexing the involved knee to the maximum flexion point possible. The subject was asked to respond to the following question: "On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, how much pain did you have while bending your knee?"

End point type	Primary

End point timeframe:

0 to 96 hours

End point values	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg	SKY0402 600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	26	25
Units: Units on a scale*hours				
arithmetic mean (standard deviation)	20.7 (± 5.4)	19.5 (± 5.3)	18.8 (± 5.3)	19.1 (± 4.4)

End point values	0.25% Bupivacaine HCl 150mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Units on a scale*hours				
arithmetic mean (standard deviation)	20.4 (± 3.9)			

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis: NRS-A AUC through Day 4
Comparison groups	SKY0402 150mg v SKY0402 300mg v SKY0402 450 mg v SKY0402 600mg v 0.25% Bupivacaine HCl 150mg
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8198 [1]
Method	ANOVA
Parameter estimate	Adjusted Mean
Confidence interval	
level	95 %
Variability estimate	Standard error of the mean

Notes:

[1] - P-Values per arm: 150mg=0.8198; 300mg=0.4827; 450mg=0.1926; 600mg=0.3125

Secondary: Number of participants with Adverse Events or Serious Adverse Events through 30 days

End point title	Number of participants with Adverse Events or Serious Adverse Events through 30 days

End point description:

End point type	Secondary

End point timeframe:

Up to 30 days

End point values	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg	SKY0402 600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	26	25
Units: Participants	23	19	16	25

End point values	0.25% Bupivacaine HCl 150mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Participants	29			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded through Day 8; serious adverse events (SAEs) were recorded through Day 36.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	SKY0402 150mg
Reporting group description: -	
Reporting group title	SKY0402 300mg
Reporting group description: -	
Reporting group title	SKY0402 450 mg
Reporting group description: -	
Reporting group title	SKY0402 600mg
Reporting group description: -	
Reporting group title	0.25% Bupivacaine HCl 150mg

Reporting group description: -

Serious adverse events	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	2 / 26 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 26 (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			
Sedation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			

subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
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			
Hypoxia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory depression			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			

subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SKY0402 600mg	0.25% Bupivacaine HCl 150mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)	3 / 35 (8.57%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events		0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sedation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory depression			

subjects affected / exposed	0 / 25 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (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			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SKY0402 150mg	SKY0402 300mg	SKY0402 450 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	19 / 25 (76.00%)	16 / 26 (61.54%)
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	7 / 27 (25.93%)	4 / 25 (16.00%)	2 / 26 (7.69%)
occurrences (all)	7	4	2
Vascular disorders			
Hypotension			

subjects affected / exposed	6 / 27 (22.22%)	6 / 25 (24.00%)	2 / 26 (7.69%)
occurrences (all)	6	6	2
Hypertension			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 27 (14.81%)	5 / 25 (20.00%)	2 / 26 (7.69%)
occurrences (all)	4	5	2
Bradycardia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	0 / 26 (0.00%)
occurrences (all)	3	3	0
Somnolence			
subjects affected / exposed	6 / 27 (22.22%)	2 / 25 (8.00%)	3 / 26 (11.54%)
occurrences (all)	6	2	3
Headache			
subjects affected / exposed	2 / 27 (7.41%)	1 / 25 (4.00%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Lethargy			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Hypoaesthesia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 27 (33.33%)	11 / 25 (44.00%)	8 / 26 (30.77%)
occurrences (all)	9	11	8
Oedema peripheral			
subjects affected / exposed	8 / 27 (29.63%)	7 / 25 (28.00%)	2 / 26 (7.69%)
occurrences (all)	8	7	2
Fatigue			

subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Asthenia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 25 (4.00%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
haemorrhagic anaemia			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	2 / 26 (7.69%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 27 (44.44%)	8 / 25 (32.00%)	9 / 26 (34.62%)
occurrences (all)	13	8	9
Constipation			
subjects affected / exposed	10 / 27 (37.04%)	11 / 25 (44.00%)	3 / 26 (11.54%)
occurrences (all)	10	11	3
Vomiting			
subjects affected / exposed	6 / 27 (22.22%)	2 / 25 (8.00%)	4 / 26 (15.38%)
occurrences (all)	6	2	4
Dyspepsia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	12	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	1 / 26 (3.85%)
occurrences (all)	3	3	1
Blister			
subjects affected / exposed	1 / 27 (3.70%)	3 / 25 (12.00%)	0 / 26 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			

Muscle spasms			
subjects affected / exposed	4 / 27 (14.81%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	4	2	0
Joint swelling			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1

Non-serious adverse events	SKY0402 600mg	0.25% Bupivacaine HCl 150mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	29 / 35 (82.86%)	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 25 (0.00%)	7 / 35 (20.00%)	
occurrences (all)	0	7	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 25 (28.00%)	12 / 35 (34.29%)	
occurrences (all)	7	14	
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	7 / 25 (28.00%)	4 / 35 (11.43%)	
occurrences (all)	7	4	
Bradycardia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 25 (28.00%)	6 / 35 (17.14%)	
occurrences (all)	7	6	
Somnolence			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 25 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Lethargy			
subjects affected / exposed	3 / 25 (12.00%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 25 (40.00%)	11 / 35 (31.43%)	
occurrences (all)	10	11	
Oedema peripheral			
subjects affected / exposed	13 / 25 (52.00%)	11 / 35 (31.43%)	
occurrences (all)	13	11	
Fatigue			
subjects affected / exposed	2 / 25 (8.00%)	4 / 35 (11.43%)	
occurrences (all)	2	4	
Asthenia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Chills			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
haemorrhagic anaemia			
subjects affected / exposed	12 / 25 (48.00%)	6 / 35 (17.14%)	
occurrences (all)	12	6	
Anaemia			
subjects affected / exposed	5 / 25 (20.00%)	2 / 35 (5.71%)	
occurrences (all)	5	2	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	19 / 25 (76.00%)	23 / 35 (65.71%)	
occurrences (all)	20	25	
Constipation			
subjects affected / exposed	12 / 25 (48.00%)	13 / 35 (37.14%)	
occurrences (all)	12	13	
Vomiting			
subjects affected / exposed	4 / 25 (16.00%)	6 / 35 (17.14%)	
occurrences (all)	4	6	
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 25 (12.00%)	6 / 35 (17.14%)	
occurrences (all)	3	6	
Blister			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 25 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Joint swelling			
subjects affected / exposed	3 / 25 (12.00%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	2	1	

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