

**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
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00485693
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	Clinical Operations, Pacira Pharmaceuticals, Inc., +1 858-625-2424, medinfo@pacira.com
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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



## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Inclusion: Male or Female  $\geq 18$  and  $\leq 75$ , 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
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<b>Arm title</b>	SKY0402 150mg
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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

<b>Arm title</b>	SKY0402 300mg
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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

<b>Arm title</b>	SKY0402 450 mg
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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

<b>Arm title</b>	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

<b>Arm title</b>	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

<b>Number of subjects in period 1</b>	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	-	-	-

<b>Number of subjects in period 1</b>	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

<b>Statistical analysis title</b>	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	

<b>End point values</b>	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

<b>End point values</b>	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
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### 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:	-

<b>Serious adverse events</b>	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
<b>Respiratory, thoracic and mediastinal disorders</b>			
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
<b>Psychiatric disorders</b>			
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
<b>Renal and urinary disorders</b>			
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
<b>Infections and infestations</b>			
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

<b>Serious adverse events</b>	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	
<b>Psychiatric disorders</b>			
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	
<b>Renal and urinary disorders</b>			
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	
<b>Infections and infestations</b>			
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 %

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

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

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

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

<b>Non-serious adverse events</b>	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 occurrences (all)	0 / 25 (0.00%) 0	7 / 35 (20.00%) 7	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)  Hypertension subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7  0 / 25 (0.00%) 0	12 / 35 (34.29%) 14  1 / 35 (2.86%) 1	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)  Bradycardia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7  2 / 25 (8.00%) 2	4 / 35 (11.43%) 4  1 / 35 (2.86%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Somnolence	7 / 25 (28.00%) 7	6 / 35 (17.14%) 6	

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

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

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported