Clinical trial results:
Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years.

Summary

EudraCT number	2014-000623-24
Trial protocol	GB PL
Global end of trial date	03 November 2016

Results information

Result version number	v1
This version publication date	05 May 2017
First version publication date	05 May 2017

Trial information

Trial identification

Sponsor protocol code	KF5503-72

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02221674
WHO universal trial number (UTN)	U1111-1153-1662
Other trial identifiers	R331333PAI2007: Depomed Inc.

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 241569 3223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 241569 3223, Clinical-Trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000018-PIP01-07
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	17 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2016
Global end of trial reached?	Yes
Global end of trial date	03 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide after the administration of a single dose of tapentadol oral solution in children aged from birth to less than 2 years after a surgical procedure that routinely produces moderate to severe acute post-surgical pain requiring opioid treatment. The concentration data will be used to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach. This will enable data based recommendations for the use of tapentadol in children of different ages in subsequent safety and efficacy trials.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local law, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
Subjects have been confined to the trial site until completion of End of Treatment assessments.
This trial has been designed to protect the interests of the child subjects, including minimizing the risk to subjects and ensuring compliance with the recommendations made by an EMEA ad hoc working party (2008) regarding the amount of blood to be drawn as well as the monitoring of children in a controlled environment (post-operative setting that provides intensive monitoring).

Background therapy:

During surgery and peri-operatively, the use of pre-medications, intraoperative medications, and opioid analgesics were allowed according to the usual standard of care. Non-opioid analgesics were allowed after the end of surgery/anesthesia according to medical judgment and standard of care.
Medications for the treatment of adverse events were allowed according to the investigator’s judgment and post-operative standard of care

Evidence for comparator:

Not applicable.

Actual start date of recruitment	05 November 2015
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	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	19
EEA total number of subjects	4

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	15
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject signed informed consent on the 05 Nov 2014 and the last subject completed the trial on the 03 Nov 2016.
The trial followed a staggered recruitment, starting with the recruitment of subjects in the oldest age group. Exposure and safety of at least 2 subjects had been assessed before enrollment in the next younger age group started.

Pre-assignment

Screening details:

The parents of a total of 40 subjects signed an informed consent and 19 of these subjects were allocated to IMP.
21 subjects dropped out before allocation to treatment: 16 subjects did not meet the inclusion and exclusion criteria, the parents of 4 subjects withdrew consent, and 1 subject was not allocated for other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Age group 1: 6 months to less than 2 years

Arm description:

Infant and toddlers aged 6 months to less than 2 years at the time of allocation to IMP.

Arm type	Experimental
Investigational medicinal product name	Tapentadol oral solution
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of tapentadol oral solution postoperatively. The dose administered depended on the age of the subject and the body weight.
Subjects aged 6 months to less than 2 years received a dose of 0.75 mg/kg. The dose and volume has been appropriately rounded if necessary.

Arm title	Age group 2: 1 month to less than 6 months

Arm description:

Infants aged 1 month to less than 6 months at the time of allocation to IMP.

Arm type	Experimental
Investigational medicinal product name	Tapentadol oral solution
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of tapentadol oral solution postoperatively. The dose administered depended on the age of the subject and the body weight.

Subjects aged 1 month to less than 6 months received a dose of 0.60 mg/kg. The dose and volume has been appropriately rounded if necessary.

Arm title	Age group 3: birth to less than 1 month
Arm description:	
Newborns and infants aged less than 1 month at the time of allocation to IMP.	
Arm type	Experimental
Investigational medicinal product name	Tapentadol oral solution
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of tapentadol oral solution postoperatively. The dose administered depended on the age of the subject and the body weight.
Subjects from birth to less than 1 month received a dose of 0.50 mg/kg. The dose and volume has been appropriately rounded if necessary.

Number of subjects in period 1	Age group 1: 6 months to less than 2 years	Age group 2: 1 month to less than 6 months	Age group 3: birth to less than 1 month
Started	8	6	5
Completed	7	6	5
Not completed	1	0	0
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Age group 1: 6 months to less than 2 years
Reporting group description:	
Infant and toddlers aged 6 months to less than 2 years at the time of allocation to IMP.	
Reporting group title	Age group 2: 1 month to less than 6 months
Reporting group description:	
Infants aged 1 month to less than 6 months at the time of allocation to IMP.	
Reporting group title	Age group 3: birth to less than 1 month
Reporting group description:	
Newborns and infants aged less than 1 month at the time of allocation to IMP.	

Reporting group values	Age group 1: 6 months to less than 2 years	Age group 2: 1 month to less than 6 months	Age group 3: birth to less than 1 month
Number of subjects	8	6	5
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	420	92.8	14.6
standard deviation	± 147.8	± 37.9	± 8.5
Gender categorical Units: Subjects			
Female	4	2	3
Male	4	4	2
Height Units: centimeter			
arithmetic mean	73.3	62	53.4
standard deviation	± 5.2	± 4.3	± 4.4
Weight Units: kilogram(s)			
arithmetic mean	9.21	5.92	3.78
standard deviation	± 1.5	± 1.18	± 0.66
Body Mass index Units: kilogram(s)/square meter			
arithmetic mean	17.11	15.28	13.36
standard deviation	± 1.36	± 1.31	± 2.49

Reporting group values	Total		
Number of subjects	19		
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean			

standard deviation	-		

Gender categorical Units: Subjects			
Female	9		
Male	10		
Height Units: centimeter			
arithmetic mean			
standard deviation	-		
Weight Units: kilogram(s)			
arithmetic mean			
standard deviation	-		
Body Mass index Units: kilogram(s)/square meter			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Age group 1: 6 months to less than 2 years
Reporting group description:	
Infant and toddlers aged 6 months to less than 2 years at the time of allocation to IMP.	
Reporting group title	Age group 2: 1 month to less than 6 months
Reporting group description:	
Infants aged 1 month to less than 6 months at the time of allocation to IMP.	
Reporting group title	Age group 3: birth to less than 1 month
Reporting group description:	
Newborns and infants aged less than 1 month at the time of allocation to IMP.	
Subject analysis set title	Age group 1_ Pharmacokinetic Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects of age group 1 who had quantifiable serum concentrations.	
Subject analysis set title	Age group 2_ Pharmacokinetic Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects of age group 2 who had quantifiable serum concentrations.	
Subject analysis set title	Age group 3_ Pharmacokinetic Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects of age group 3 who had quantifiable serum concentrations.	

Primary: Age group 1: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution

End point title	Age group 1: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution[1]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per subject.

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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 1_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	7[2]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
30 minutes after administration (N=3)	9.8 (± 5.21)			
1 hour after administration (N=1)	18.79 (± 0)			
2 hours after administration (N=2)	32.2 (± 14.92)			

4 hours after administration (N=3)	11.1 (± 5.97)			
6 hours after administration (N=1)	14.85 (± 0)			
8 hours after administration (N=2)	10.7 (± 4.15)			

Notes:

[2] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Primary: Age group 2: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution

End point title	Age group 2: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution[3]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per 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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 2_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[4]			
Units: nanogram(s)/mililitre				
arithmetic mean (standard deviation)				
30 minutes after administration (N=2)	8.3 (± 6.3)			
1 hour after administration (N=1)	35.27 (± 0)			
2 hours after administration (N=3)	27.3 (± 0.81)			
4 hours after administration (N=2)	25.9 (± 10.33)			
6 hours after administration (N=1)	32.75 (± 0)			
8 hours after administration (N=2)	5.6 (± 1.81)			

Notes:

[4] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Primary: Age group 3: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution

End point title	Age group 3: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution[5]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per subject.

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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 3_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	5[6]			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
30 minutes after administration (N=1)	26.62 (± 0)			
1 hour after administration (N=1)	43.63 (± 0)			
2 hours after administration (N=2)	19.9 (± 7.67)			
4 hours after administration (N=2)	15 (± 8.92)			
6 hours after administration (N=1)	18.82 (± 0)			
8 hours after administration (N=2)	14.6 (± 6.26)			

Notes:

[6] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Primary: Age group 1: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution

End point title	Age group 1: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution[7]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per subject.

Notes:

[7] - 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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 1_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	7[8]			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				

30 minutes after administration (N=3)	105.7 (± 125)			
1 hour after administration (N=1)	430.7 (± 0)			
2 hours after administration (N=2)	468 (± 248.41)			
4 hours after administration (N=3)	348.7 (± 228.22)			
6 hours after administration (N=1)	370.2 (± 0)			
8 hours after administration (N=2)	285.1 (± 107.06)			

Notes:

[8] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Primary: Age group 2: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution

End point title	Age group 2: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution[9]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per subject.

Notes:

[9] - 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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 2_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[10]			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
30 minutes after administration (N=1)	128.8 (± 0)			
1 hour after administration (N=1)	136.3 (± 0)			
2 hours after administration (N=3)	324.9 (± 116.61)			
4 hours after administration (N=2)	449.7 (± 7.42)			
6 hours after administration (N=1)	253.3 (± 0)			
8 hours after administration (N=2)	92.2 (± 63.83)			

Notes:

[10] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Primary: Age group 3: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution

End point title	Age group 3: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide after a Single Dose of Tapentadol Oral Solution[11]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.

End point type	Primary

End point timeframe:

Up to 8 hours after IMP administration at two time points per subject.

Notes:

[11] - 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: The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide to characterize the pharmacokinetic parameters of tapentadol using a population and physiologically-based pharmacokinetic approach.

End point values	Age group 3_ Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	5[12]			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
30 minutes after administration (N=1)	74.38 (± 0)			
1 hour after administration (N=1)	209 (± 0)			
2 hours after administration (N=2)	98.5 (± 2.62)			
4 hours after administration (N=2)	147.6 (± 53.74)			
6 hours after administration (N=1)	224.8 (± 0)			
8 hours after administration (N=2)	174.1 (± 11.03)			

Notes:

[12] - Summary statistics were only calculated when there were 2 or more samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in pain intensity using the Face, Legs, Activity, Cry, Consolability scale (FLACC)

End point title	Change in pain intensity using the Face, Legs, Activity, Cry, Consolability scale (FLACC)

End point description:

The change from baseline in pain intensity using the Face, Legs, Activity, Cry, Consolability Scale (FLACC Scale) at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 15 hours after dosing with tapentadol.
The FLACC Scale was developed by the Department of Anesthesiology, University of Michigan Medical School and Health Systems. It is a behavioral scale for scoring postoperative pain in young children. This tool includes five categories of pain behaviors, including facial expression, leg movement, activity, cry, and consolability. Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

End point type	Secondary

End point timeframe:

Predose, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 15 hours

after dosing with tapentadol.

End point values	Age group 1: 6 months to less than 2 years	Age group 2: 1 month to less than 6 months	Age group 3: birth to less than 1 month	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[13]	6	5	
Units: units on a scale				
arithmetic mean (standard deviation)				
+ 15 min	-0.8 (± 3.1)	-1.3 (± 2.8)	-1.6 (± 1.5)	
+ 30 min	-1.1 (± 2.6)	-3 (± 3.6)	-1.4 (± 1.5)	
+ 1 hour	-2 (± 3.6)	-2.7 (± 4.5)	0 (± 3.7)	
+ 2 hours	-2.8 (± 2.9)	-3 (± 3.9)	-0.4 (± 2.6)	
+ 4 hours	-1.6 (± 3.4)	-2.2 (± 3.3)	-0.4 (± 2.3)	
+ 6 hours	-1.9 (± 3.1)	-1.7 (± 4.8)	-0.4 (± 2.3)	
+ 8 hours	-2.5 (± 2.5)	-3 (± 3.2)	-1.2 (± 1.1)	
+ 12 hours	-2.4 (± 2.8)	-3.5 (± 3.8)	-1.4 (± 1.5)	
+ 15 hours	-2.1 (± 3.5)	-3.8 (± 3.9)	-1 (± 2.1)	

Notes:

[13] - For the timepoint "+ 6 hours" only 7 values were collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event starting at, or worsened at or after the time of the single dose administration of tapentadol until the time of the subject-related end of trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Age group 1: 6 months to less than 2 years

Reporting group description:

Infant and toddlers aged 6 months to less than 2 years at the time of allocation to IMP.

Reporting group title	Age group 2: 1 month to less than 6 months

Reporting group description:

Infants aged 1 month to less than 6 months at the time of allocation to IMP.

Reporting group title	Age group 3: birth to less than 1 month

Reporting group description:

Newborns and infants aged less than 1 month at the time of allocation to IMP.

Reporting group title	Overall

Reporting group description: -

Serious adverse events	Age group 1: 6 months to less than 2 years	Age group 2: 1 month to less than 6 months	Age group 3: birth to less than 1 month
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Age group 1: 6 months to less than 2 years	Age group 2: 1 month to less than 6 months	Age group 3: birth to less than 1 month
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	3 / 6 (50.00%)	2 / 5 (40.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Stoma site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Wound dehiscence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Junctional ectopic tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Stoma site erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Wound dehiscence			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cardiac disorders			

Junctional ectopic tachycardia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 2 / 19 (10.53%) 2		
Respiratory, thoracic and mediastinal disorders Tachypnoea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2015	Adapted inclusion and exclusion criteria and certain study procedures to better align with the "standard of care" procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported