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

Summary

EudraCT number	2014-002259-24
Trial protocol	HU PL GB ES CZ FR DE
Global end of trial date	27 September 2018

Results information

Result version number	v2 (current)
This version publication date	16 February 2019
First version publication date	13 July 2017
Version creation reason	• New data added to full data set • Correction of full data set - Completion of dataset for Subgroup 4

Trial information

Trial identification

Sponsor protocol code	KF5503-73

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1157-3228

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, +49 241569 3223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Clinical Trial Helpdesk, 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	02 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2018
Global end of trial reached?	Yes
Global end of trial date	27 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide after the administration of a single dose of intravenous tapentadol solution for injection (tapentadol IV) in children aged from birth to less than 2 years, including preterm neonates, after a qualifying procedure that routinely produced moderate to severe acute pain requiring opioid treatment. The concentration data was to be used to characterize the pharmacokinetic parameters of tapentadol using a population pharmacokinetic approach. This was to enable data-based recommendations for the use of tapentadol in children of different ages.

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.
The competent authorities approved the trial as required by national regulations.
Regulatory authorities were notified of the trial and amendments as required by national regulations.
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:

All prior/concomitant medication/therapies were allowed as per standard of care, unless a medication was explicitly prohibited. Medications for the treatment of adverse events were allowed according to the investigator’s judgment and post-operative standard of care.
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.

Evidence for comparator:

NA

Actual start date of recruitment	23 April 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	Spain: 1
Country: Number of subjects enrolled	Poland: 36

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 6
Worldwide total number of subjects	46
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	10
Newborns (0-27 days)	10
Infants and toddlers (28 days-23 months)	26
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 was enrolled on 23 Apr 2015 and last subject for the final analysis completed the trial on 27 Sep 2018. The trial followed a staggered recruitment, starting with the recruitment of subjects in the eldest age group. Exposure and safety of at least 4 subjects had been assessed before enrollment in the next younger age group started.

Pre-assignment

Screening details:

The parents of 46 subjects signed an informed consent; 40 subjects were allocated to tapentadol IV, 38 were treated.
6 subjects dropped out before allocation to treatment and 2 subjects after allocation but before receiving tapentadol IV: 6 subjects did not meet inclusion and exclusion criteria and the parents of 2 subjects withdrew consent.

Pre-assignment period milestones

Number of subjects started	46
Number of subjects completed	38

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion criteria not met/exclusion criteria met: 6
Reason: Number of subjects	Parents of subjects withdrew consent: 2

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:

Infants and toddlers aged 6 months to less than 2 years at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.

Arm type	Experimental
Investigational medicinal product name	Tapentadol solution for injection
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of tapentadol solution for injection as a continuous, constant-rate, intravenous infusion over 1 hour.
The dose administered depended on the gestational and postnatal age.
Subjects aged 6 months to less than 2 years were to receive a dose of 0.4 mg/kg.
The IMP has been given when the subject was considered clinically stable.

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 who received any amount of intravenous tapentadol solution for injection.

Arm type	Experimental
Investigational medicinal product name	Tapentadol solution for injection
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of tapentadol solution for injection as a continuous, constant-rate, intravenous infusion over 1 hour.
The dose administered depended on the gestational and postnatal age.
Subjects aged 1 month to less than 6 months were to receive a dose of 0.4 mg/kg.
The IMP has been given when the subject was considered clinically stable.

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

Arm description:

Newborns and infants from birth (must be of at least 37 weeks gestational age) to less than 1 month at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.

Arm type	Experimental
Investigational medicinal product name	Tapentadol solution for injection
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of tapentadol solution for injection as a continuous, constant-rate, intravenous infusion over 1 hour.
The planned dose to be administered depended on the gestational and postnatal age.
Subjects with a postnatal age of equal or more than 7 days were to receive a dose of 0.4 mg/kg.
Subjects with a postnatal age of less than 7 days were to receive a dose of 0.3 mg/kg.
The IMP has been given when the subject was considered clinically stable.

Arm title	Age group 4: preterm born subjects

Arm description:

Preterm born subjects from birth with a postmenstrual age of equal or less than 41 weeks and a gestational age of 24 weeks to less than 37 weeks at the time of allocation to IMP, who received any amount of intravenous tapentadol solution for injection.

Arm type	Experimental
Investigational medicinal product name	Tapentadol solution for injection
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of tapentadol solution for injection as a continuous, constant-rate, intravenous infusion over 1 hour.
Depending on their gestational age and postnatal age, subjects were to receive a dose of either 0.3 mg/kg or 0.4 mg/kg as per dosing instruction in the protocol.
The IMP has been given when the subject was considered clinically stable.

Number of subjects in period 1[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	10	11	9
Completed	10	11	9

Number of subjects in period 1[1]	Age group 4: preterm born subjects
Started	8
Completed	8

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The pre-assignment period gives details for all subjects that signed an informed consent but were not treated.

Baseline characteristics

Reporting groups	
Reporting group title	Age group 1: 6 months to less than 2 years
Reporting group description:	
Infants and toddlers aged 6 months to less than 2 years at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.	
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 who received any amount of intravenous tapentadol solution for injection.	
Reporting group title	Age group 3: birth to less than 1 month
Reporting group description:	
Newborns and infants from birth (must be of at least 37 weeks gestational age) to less than 1 month at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.	
Reporting group title	Age group 4: preterm born subjects
Reporting group description:	
Preterm born subjects from birth with a postmenstrual age of equal or less than 41 weeks and a gestational age of 24 weeks to less than 37 weeks at the time of allocation to IMP, who received any amount of intravenous tapentadol solution for injection.	

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	10	11	9
Age categorical			
Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	9
Infants and toddlers (28 days-23 months)	10	11	0
Age continuous			
Units: days			
arithmetic mean	423	95.2	15.3
standard deviation	± 158.4	± 41.8	± 6.4
Gender categorical			
Units: Subjects			
Female	0	4	2
Male	10	7	7
Height			
Units: centimeter			
arithmetic mean	82.1	62.7	53.6
standard deviation	± 8.2	± 7.2	± 4.4
Weight			
Units: kilogram(s)			
arithmetic mean	11.16	6.36	3.68
standard deviation	± 2.18	± 1.64	± 0.58
Body Mass index			
Units: kilogram(s)/square meter			
arithmetic mean	16.48	15.95	12.82
standard deviation	± 1.53	± 1.86	± 1.31

Gestational Age			
Gestational age was only required for subgroups 3 and 4.			
Units: weeks			
arithmetic mean	0	0	38.2
standard deviation	± 0	± 0	± 1.2
Postmenstrual age			
Post menstrual age was only required for subgroup 4.			
Units: weeks			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
FLACC (Face, Legs, Activity,Cry, Consolability) scale			
The pre-dose measurement was used as baseline value for calculation of change in pain intensity. 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.			
Units: units on a scale			
arithmetic mean	4.7	4.9	3.8
standard deviation	± 3.2	± 1.9	± 2.6

Reporting group values	Age group 4: preterm born subjects	Total	
Number of subjects	8	38	
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	8	8	
Newborns (0-27 days)	0	9	
Infants and toddlers (28 days-23 months)	0	21	
Age continuous Units: days			
arithmetic mean	35.0		
standard deviation	± 37.7	-	
Gender categorical Units: Subjects			
Female	4	10	
Male	4	28	
Height Units: centimeter			
arithmetic mean	48.8		
standard deviation	± 3.8	-	
Weight Units: kilogram(s)			
arithmetic mean	2.51		
standard deviation	± 0.76	-	
Body Mass index Units: kilogram(s)/square meter			
arithmetic mean	10.39		
standard deviation	± 2.12	-	
Gestational Age			

Gestational age was only required for subgroups 3 and 4.			
Units: weeks			
arithmetic mean	30.9		
standard deviation	± 4.3	-	
Postmenstrual age			
Post menstrual age was only required for subgroup 4.			
Units: weeks			
arithmetic mean	35.6		
standard deviation	± 3.0	-	
FLACC (Face, Legs, Activity,Cry, Consolability) scale			
The pre-dose measurement was used as baseline value for calculation of change in pain intensity. 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.			
Units: units on a scale			
arithmetic mean	2.9		
standard deviation	± 2.5	-	

End points

End points reporting groups

Reporting group title	Age group 1: 6 months to less than 2 years
Reporting group description:	
Infants and toddlers aged 6 months to less than 2 years at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.	
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 who received any amount of intravenous tapentadol solution for injection.	
Reporting group title	Age group 3: birth to less than 1 month
Reporting group description:	
Newborns and infants from birth (must be of at least 37 weeks gestational age) to less than 1 month at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.	
Reporting group title	Age group 4: preterm born subjects
Reporting group description:	
Preterm born subjects from birth with a postmenstrual age of equal or less than 41 weeks and a gestational age of 24 weeks to less than 37 weeks at the time of allocation to IMP, who received any amount of intravenous tapentadol solution for injection.	

Primary: Serum Concentrations of Tapentadol after a single dose of tapentadol solution for injection

End point title	Serum Concentrations of Tapentadol after a single dose of tapentadol solution for injection[1]
End point description:	
Pharmacokinetic evaluation based on serum concentrations of tapentadol from blood samples taken within 10 hours of a single dose of IMP administration at 3 time points per subject. Subjects have been allocated to one of 4 different blood sampling schedules as per protocol. Serum pharmacokinetic samples have been analyzed to determine concentrations of tapentadol using validated liquid chromatography-tandem mass spectrometry bioanalytical assays. All subjects who had quantifiable serum concentrations have been included in the descriptive pharmacokinetic analysis. Summary statistics were only be determined if at least 2 observations per time point were above lower limit of quantification. SD has not been calculated if N = 1.	
End point type	Primary
End point timeframe:	
up to 10 hours	

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: Serum concentration analyzed for 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	Age group 4: preterm born subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[2]	11[3]	9[4]	8[5]
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
15 min after start of IMP (N=4/4/3/2)	188 (± 332.44)	18.2 (± 12.63)	51.0 (± 61.76)	30.5 (± 3.27)
30 min after start of IMP (N=2/3/2/2)	46.2 (± 16.00)	38.2 (± 11.03)	25.7 (± 9.4)	23.9 (± 9.33)
1 hour after start of IMP (N=4/4/3/2)	68.9 (± 23.72)	51.4 (± 19.69)	56.8 (± 14.29)	37.5 (± 28.73)
1.25 hour after start of IMP (N=2/2/2/2)	57.7 (± 14.47)	67.2 (± 15.87)	38.6 (± 3.68)	26.1 (± 16.07)

1.5 hour after start of IMP (N=2/2/2/2)	118.1 (± 100.58)	113.1 (± 101.32)	37.5 (± 8.35)	41.3 (± 2.51)
2 hours after start of IMP (N=2/3/2/2)	46.6 (± 6.81)	45.2 (± 3.14)	37.6 (± 11.97)	29.4 (± 0.71)
3 hours after start of IMP (N=2/2/2/2)	32.5 (± 12.71)	39.3 (± 18.54)	25.7 (± 0.48)	33.6 (± 5.50)
4 hours after start of IMP (N=2/2/2/2)	17.6 (± 14.57)	35.2 (± 6.22)	19.2 (± 2.35)	12.2 (± 5.43)
6 hours after start of IMP (N=4/4/3/2)	20.9 (± 19.14)	10.2 (± 5.01)	18.3 (± 3.03)	29.7 (± 23.97)
7 hours after start of IMP (N=2/2/2/2)	10.2 (± 3.83)	17.9 (± 19.45)	12.7 (± 5.06)	22.8 (± 6.03)
8 hours after start of IMP (N=2/3/2/2)	8.6 (± 3.39)	12.7 (± 9.16)	10.7 (± 5.78)	7.6 (± 6.72)
10 hours after start of IMP (N=2/1/2/2)	12.4 (± 12.38)	11.46 (± 0)	5.3 (± 3.46)	4.4 (± 0.18)

Notes:

[2] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[3] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[4] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[5] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.

Statistical analyses

No statistical analyses for this end point

Primary: Serum Concentrations of Tapentadol-O-glucuronide after a single dose of tapentadol solution for injection

End point title	Serum Concentrations of Tapentadol-O-glucuronide after a single dose of tapentadol solution for injection[6]

End point description:

Pharmacokinetic evaluation based on serum concentrations of tapentadol O- glucuronide from blood samples taken within 10 hours of a single dose of IMP administration at 3 time points per subject.
Subjects have been allocated to one of 4 different blood sampling schedules as per protocol.
Serum pharmacokinetic samples have been analyzed to determine concentrations of tapentadol -O-glucuronide using validated liquid chromatography-tandem mass spectrometry bioanalytical assays.
All subjects who had quantifiable serum concentrations have been included in the descriptive pharmacokinetic analysis. Summary statistics were only be determined if at least 2 observations per time point were above lower limit of quantification. SD has not been calculated if N = 1.
At the 15 minutes time point the PK samples for all subjects were below the lower limit of quantification. Therefore, this time point has not been listed.

End point type	Primary

End point timeframe:

up to 10 hours

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Serum concentration analyzed for tapentadol-O-glucuronide.

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	Age group 4: preterm born subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[7]	11[8]	9[9]	8[10]
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
30 min after start of IMP (N=2/2/1/2)	24.7 (± 7.86)	19.5 (± 12.73)	12.26 (± 0)	26.3 (± 13.34)
1 hour after start of IMP (N=4/4/3/2)	90.1 (± 57.03)	81.2 (± 34.93)	63.1 (± 15.62)	157.0 (± 133.29)
1.25 hour after start of IMP (N=2/2/2/2)	213.7 (± 16.76)	128.5 (± 121.5)	208.7 (± 153.98)	59.4 (± 58.56)

1.5 hour after start of IMP (N=2/2/2/2)	108.8 (± 26.14)	165.2 (± 30.97)	92.6 (± 53.12)	54.6 (± 0.11)
2 hours after start of IMP (N=2/3/2/2)	171.8 (± 28.14)	126.9 (± 79.85)	159.4 (± 67.74)	244.9 (± 0.42)
3 hours after start of IMP (N=2/2/2/2)	171.5 (± 81.81)	186.6 (± 28.35)	153.4 (± 50.06)	92.1 (± 8.63)
4 hours after start of IMP (N=2/2/2/2)	99.2 (± 31.76)	223.5 (± 48.65)	486.4 (± 398.53)	149.8 (± 153.36)
6 hours after start of IMP (N=4/4/3/2)	99.2 (± 18.28)	158.7 (± 130.02)	267.3 (± 49.73)	117.7 (± 87.90)
7 hours after start of IMP (N=2/2/2/2)	70.0 (± 25.72)	88.4 (± 48.54)	186.6 (± 48.86)	146.3 (± 15.41)
8 hours after start of IMP (N=2/3/2/2)	115.9 (± 28.72)	99.7 (± 24.54)	221.4 (± 38.4)	222.1 (± 206.75)
10 hours after start of IMP (N=2/1/2/2)	153.6 (± 99.22)	158 (± 0)	407.5 (± 278.03)	148.1 (± 126.44)

Notes:

[7] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[8] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[9] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.
[10] - Pharmacokinetic Set
N= number of subjects with observed values per time point and age group.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The change from baseline in pain intensity was assessed using the Face, Legs, Activity, Cry, Consolability scale (FLACC scale) at 15 minutes, 30 minutes, and at 1, 2, 4, 6, 8, 12, and 15 hours after a single dose of tapentadol solution for injection.
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 and non-verbal children. This tool includes 5 categories of pain behaviors, including facial expression (F), leg movement (L), activity (A), cry (C), and consolability (C). Each of the 5 categories is scored 0, 1, or 2, which results in a total score between 0 and 10.
The pain intensity scores were summarized descriptively per scheduled time point.

End point type	Secondary

End point timeframe:

up to 15 hours

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	Age group 4: preterm born subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[11]	11[12]	9[13]	8[14]
Units: units on a scale				
arithmetic mean (standard deviation)				
+ 15 min (N=10/10/9/8)	-1.5 (± 1.7)	-2.6 (± 2.2)	-1.2 (± 3.1)	-0.9 (± 2.2)
+ 30 min (N=10/10/9/8)	-3.7 (± 2.9)	-4.3 (± 2.3)	-2.9 (± 3.0)	-0.9 (± 2.4)

+ 1 hour (N=10/10/9/8)	-4.7 (± 3.2)	-4.9 (± 1.9)	-3.6 (± 2.7)	-1.9 (± 2.9)
+ 2 hours (N=10/10/9/8)	-4.2 (± 4.0)	-4.1 (± 3.4)	-3.0 (± 3.2)	-1.9 (± 3.0)
+ 4 hours (N=10/10/9/8)	-4.6 (± 3.2)	-4.5 (± 2.1)	-2.4 (± 3.6)	-1.8 (± 2.9)
+ 6 hours (N=9/10/7/7)	-4.7 (± 2.9)	-3.7 (± 3.1)	-3.0 (± 3.2)	-1.7 (± 3.7)
+ 8 hours (N=10/10/9/8)	-4.3 (± 3.1)	-3.8 (± 3.0)	-2.2 (± 3.6)	-1.3 (± 3.7)
+ 12 hours (N=10/10/9/8)	-4.4 (± 3.3)	-4.7 (± 1.9)	-3.2 (± 3.3)	-1.9 (± 2.6)
+ 15 hours (N=10/10/9/8)	-4.7 (± 3.2)	-4.1 (± 2.1)	-2.4 (± 3.5)	-1.5 (± 2.5)

Notes:

[11] - Full Analysis Set
N= number of subjects with observed values per time point and age group.
[12] - Full Analysis Set
N= number of subjects with observed values per time point and age group.
[13] - Full Analysis Set
N= number of subjects with observed values per time point and age group.
[14] - Full Analysis Set
N= number of subjects with observed values per time point and age group.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any Adverse Events (AE) that started at or after the start of the iv administration of the IMP or starting before IMP administration and worsened in intensity after the start of the IMP up to the end of the therapeutic reach of last administration of IMP.

Adverse event reporting additional description:

The therapeutic reach is the time after treatment completion that a subject is still considered to be potentially affected by a study drug. For intravenous tapentadol solution for injection, the therapeutic reach is defined as 48 hours after the end of the IMP intake (i.e., end of IV infusion).
Adverse event were report by age group and overall.

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:

Infants and toddlers aged 6 months to less than 2 years at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.

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 who received any amount of intravenous tapentadol solution for injection.

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

Reporting group description:

Newborns and infants from birth (must be of at least 37 weeks gestational age) to less than 1 month at the time of allocation to IMP who received any amount of intravenous tapentadol solution for injection.

Reporting group title	Age group 4: preterm born subjects

Reporting group description:

Preterm born subjects from birth with a postmenstrual age of equal or less than 41 weeks and a gestational age of 24 weeks to less than 37 weeks at the time of allocation to IM, who received any amount of intravenous tapentadol solution for injection.

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 / 10 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Age group 4: preterm born subjects	Overall	
Total subjects affected by serious			

adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	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	1 / 10 (10.00%)	3 / 11 (27.27%)	5 / 9 (55.56%)
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	4
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Vaccination site injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infectious pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Non-serious adverse events	Age group 4: preterm born subjects	Overall	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	11 / 38 (28.95%)	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 8 (12.50%)	3 / 38 (7.89%)	
occurrences (all)	1	5	
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 8 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	2	
Vaccination site injury			

subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	4 / 38 (10.53%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Infections and infestations			
Infectious pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2015	- To clarify subject's discontinuation from IMP if a serious adverse event occurs or an adverse event that is detrimental to the health of a subject. - To request the documentation of the heart rate during periods of oxygen desaturation. - State that the best approximation for expected adverse drug reactions for tapentadol IV solution is provided in the adverse drug reaction table for tapentadol IR tablets in the investigator's brochure.
24 February 2016	- Specify the effect of the dead space volume of the infusion set for the IMP on the timing of subsequent assessments and blood sampling for pharmacokinetics. - Allow starting IMP before 24 hours after cardiac surgery if the subject is hemodynamically stable. - Clarify the medication restrictions for mothers of a newborn or breastfeeding mothers. - Allow other metabolites of tapentadol than tapentadol-O-glucuronide to be measured. - Adaptation of inclusion/exclusion criteria related to body weight, physical status, ECG, mechanical ventilation.
04 May 2016	- Implement dosing instructions for children aged less than 7 days old (postnatal).
17 November 2016	- The gestational age of preterm babies was widened to extend the coverage of the expected target population who will benefit from the treatment with tapentadol IV in the future. - The inclusion and exclusion criteria were adapted to better reflect the medical condition and standard of care of subjects in age subgroup 4. - The dosing instructions for children in age subgroup 4 were updated.
17 November 2016	- Due to the small blood volumes of preterm babies (age subgroup 4), blood sampling was restricted to a minimum and to align with the standard of care. - The timeline of the trial was extended. Safety experience from post-marketing data in adults was updated.
04 January 2018	- To lower the allowed gestational age from 30 weeks to 24 weeks, and supply appropriate dosing recommendations for these subjects. - To allow subjects with a painful procedure to be recruited to age subgroup 4 as an alternative to painful surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported