# 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 | v2 (current) |
| This version publication date | 14 October 2017 |
| First version publication date | 05 May 2017 |
| Version creation reason | • Correction of full data set<br>Correction of the "Timeframe for reporting adverse events" definition. |

## 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<br>Units: Subjects | | | |
| Age continuous<br>Units: days | | | |
| arithmetic mean | 420 | 92.8 | 14.6 |
| standard deviation | ± 147.8 | ± 37.9 | ± 8.5 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 2 | 3 |
| Male | 4 | 4 | 2 |
| Height<br>Units: centimeter | | | |
| arithmetic mean | 73.3 | 62 | 53.4 |
| standard deviation | ± 5.2 | ± 4.3 | ± 4.4 |
| Weight<br>Units: kilogram(s) | | | |
| arithmetic mean | 9.21 | 5.92 | 3.78 |
| standard deviation | ± 1.5 | ± 1.18 | ± 0.66 |
| Body Mass index<br>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<br>Units: Subjects | | | |
| Age continuous<br>Units: days | | | |
| arithmetic mean | | | |

| | | | |
|---|---|---|---|
| standard deviation | - | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 9 | | |
| Male | 10 | | |
| Height<br>Units: centimeter | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weight<br>Units: kilogram(s) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Body Mass index<br>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 Events that started on the intake of the IMP (investigational medicinal product) up to the end of the therapeutic reach of the IMP.
Any pre-treatment AE which worsened after IMP administration intake have been recorded as a new AE.

Adverse event reporting additional description:

The therapeutic reach is the time after IMP intake that a subject is still considered to be potentially affected by a study drug.
For tapentadol oral solution, the therapeutic reach is defined as 48 hours after (last) IMP intake.

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported