



Clinical trial results:

Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-020380-20 |
| Trial protocol | Outside EU/EEA ES |
| Global end of trial date | 23 March 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 23 June 2016 |
| First version publication date | 28 January 2015 |
| Version creation reason | • Correction of full data set Review the data |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | R331333-PAI2005 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01134536 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Janssen Research & Development, L.L.C. |
| Sponsor organisation address | Archimedesweg 29, CM Leiden, Netherlands, 2333 |
| Public contact | Clinical Registry Group, Janssen Research & Development, L.L.C., ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Janssen Research & Development, L.L.C., ClinicalTrialsEU@its.jnj.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-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 | 23 March 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 23 March 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic profile of Tapentadol and its major metabolite Tapentadol-O-glucuronide after administration of a single dose of Tapentadol oral solution (OS) 1 mg/kg in children and adolescents aged from 6 to less than 18 years after scheduled surgical procedures that routinely produce acute, moderate to severe post-surgical pain.

Protection of trial subjects:

Safety evaluations were based upon the incidence, intensity, and relationship with tapentadol of adverse events (AEs) reported throughout the study, and on changes in vital signs measurements, physical examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory tests. Any clinically important abnormalities persisting at the end of the study were followed by the investigator until resolution or a clinically stable condition was reached.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 12 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | United States: 32 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 10 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 14 |
| Adolescents (12-17 years) | 30 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 32 centers in Canada, Spain, and the United States.

Period 1

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

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1 (12-<18 years) |

Arm description:

Children with a body weight less than 20 kilogram (kg) were dosed with a single dose of tapentadol 1 milligram per kilogram (mg/kg) oral solution (OS) and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant).

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tapentadol Hydrochloride |
| Investigational medicinal product code | CG5503/R331333 |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Children with a body weight less than 20 kilogram (kg) were dosed with a single dose of tapentadol 1 milligram per kilogram (mg/kg) oral solution (OS) and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant).

| | |
|------------------|-----------------------|
| Arm title | Group 2 (6-<12 years) |
|------------------|-----------------------|

Arm description:

Children with a body weight less than 20 kg were dosed with a single dose of tapentadol 1 mg/kg OS and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant).

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tapentadol Hydrochloride |
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Dosage and administration details:

Children with a body weight less than 20 kilogram (kg) were dosed with a single dose of tapentadol 1 milligram per kilogram (mg/kg) oral solution (OS) and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant).

| Number of subjects in period 1 | Group 1 (12-<18 years) | Group 2 (6-<12 years) |
|--|------------------------|-----------------------|
| Started | 30 | 14 |
| Completed | 25 | 13 |
| Not completed | 5 | 1 |
| Subject Vomited Within 3 Hours After Study Agent A | 5 | - |
| Due to Protocol Defined Criteria to Discontinue | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | Group 1 (12-<18 years) |
| Reporting group description: Children with a body weight less than 20 kilogram (kg) were dosed with a single dose of tapentadol 1 milligram per kilogram (mg/kg) oral solution (OS) and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant). | |
| Reporting group title | Group 2 (6-<12 years) |
| Reporting group description: Children with a body weight less than 20 kg were dosed with a single dose of tapentadol 1 mg/kg OS and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant). | |

| Reporting group values | Group 1 (12-<18 years) | Group 2 (6-<12 years) | Total |
|---|------------------------|-----------------------|-------|
| Number of subjects | 30 | 14 | 44 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 14 | 14 |
| Adolescents (12-17 years) | 30 | 0 | 30 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 14.9 | 8.7 | |
| standard deviation | ± 1.68 | ± 1.68 | - |
| Title for Gender Units: subjects | | | |
| Female | 16 | 8 | 24 |
| Male | 14 | 6 | 20 |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Group 1 (12-<18 years) |
| Reporting group description: | |
| Children with a body weight less than 20 kilogram (kg) were dosed with a single dose of tapentadol 1 milligram per kilogram (mg/kg) oral solution (OS) and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant). | |
| Reporting group title | Group 2 (6-<12 years) |
| Reporting group description: | |
| Children with a body weight less than 20 kg were dosed with a single dose of tapentadol 1 mg/kg OS and children with a body weight of 20 kg or greater were dosed with a single dose of tapentadol 1 mg/kg OS (single dose of tapentadol was not exceeded 75 mg for any participant). | |
| Subject analysis set title | Pharmacokinetic Analysis Population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Pharmacokinetic analysis set included all participants with available serum concentrations. | |
| Subject analysis set title | Safety Analysis Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety analysis population included all participants who received a dose of open-label tapentadol and contributed any safety data after the start of study treatment. | |

Primary: Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum

| | |
|---|---|
| End point title | Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum ^[1] |
| End point description: | |
| Serum concentrations of tapentadol and its major metabolite tapentadol-O-glucuronide were assessed for each participant during the 15-hour post-dose evaluation phase. | |
| End point type | Primary |
| End point timeframe: | |
| 5 minutes (min) to less than (<) 30 min, 30 min to <45 min, 45 min to <1 hour (h), 1 h to <1.5 h, 1.5h to <2h, 2h to <3h, 3h to <4h, 4h to <5h, 5h to <6h, 6h to <8h, 8h to <12h, greater than (>) 12h up to 15 h post-dose | |
| 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: Descriptive statistics were done, no inferential statistical analyses were performed OR No statistical analysis were performed for this endpoint. | |

| End point values | Pharmacokinetic Analysis Population | | | |
|--|-------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 44 | | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tapentadol: 5 min to <30 min (n=10) | 10.9 (± 13.8) | | | |
| Tapentadol: 30 min to <45 min (n=19) | 39.1 (± 32.4) | | | |
| Tapentadol: 45 min to <1h (n=10) | 59.2 (± 26.7) | | | |
| Tapentadol: 1h to <1.5h (n=16) | 51.5 (± 26.3) | | | |
| Tapentadol: 1.5h to <2h (n=1) | 66.8 (± 0) | | | |

| | | | | |
|---|---------------|--|--|--|
| Tapentadol: 2h to <3h (n=12) | 47.1 (± 21.9) | | | |
| Tapentadol: 3h to <4h (n=10) | 34.4 (± 8.46) | | | |
| Tapentadol: 4h to <5h (n=17) | 30.1 (± 13.6) | | | |
| Tapentadol: 5h to <6h (n=6) | 26.5 (± 9.39) | | | |
| Tapentadol: 6h to <8h (n=9) | 18 (± 7.88) | | | |
| Tapentadol: 8h to <12h (n=22) | 6.97 (± 3.89) | | | |
| Tapentadol: >12h (n=22) | 4.26 (± 2.95) | | | |
| Tapentadol Metabolite: 5 min to <30 min (n=8) | 203 (± 183) | | | |
| Tapentadol Metabolite: 30 min to <45 min (n=18) | 834 (± 706) | | | |
| Tapentadol Metabolite: 45 min to <1h (n=10) | 1250 (± 460) | | | |
| Tapentadol Metabolite: 1h to <1.5h (n=15) | 1033 (± 441) | | | |
| Tapentadol Metabolite: 1.5h to <2h (n=1) | 1840 (± 0) | | | |
| Tapentadol Metabolite: 2h to <3h (n=12) | 1241 (± 489) | | | |
| Tapentadol Metabolite: 3h to <4h (n=10) | 1110 (± 359) | | | |
| Tapentadol Metabolite: 4h to <5h (n=17) | 769 (± 287) | | | |
| Tapentadol Metabolite: 5h to <6h (n=6) | 714 (± 237) | | | |
| Tapentadol Metabolite: 6h to <8h (n=9) | 402 (± 210) | | | |
| Tapentadol Metabolite: 8h to <12h (n=22) | 167 (± 91.8) | | | |
| Tapentadol Metabolite: >12h (n=21) | 93.7 (± 66.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) or Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Adverse Events (AEs) or Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening up to end of study (Day 2)

| | | | | |
|-----------------------------|----------------------------|--|--|--|
| End point values | Safety Analysis Population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 44 | | | |
| Units: Participants | | | | |
| AE | 20 | | | |
| SAE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Supplemental Analgesic Medication

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|-----------------|---|
| End point title | Number of Participants with Supplemental Analgesic Medication |
|-----------------|---|

End point description:

Number of participants who received supplemental postoperative analgesic medications during the 15-hour post-dose evaluation period was reported.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 15 h post-dose

| | | | | |
|-----------------------------|----------------------------|--|--|--|
| End point values | Safety Analysis Population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 44 | | | |
| Units: Participants | 32 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: McGrath Color Analog Scale (CAS) Score

| | |
|-----------------|--|
| End point title | McGrath Color Analog Scale (CAS) Score |
|-----------------|--|

End point description:

The McGrath CAS confirmed pain assessments from children by a triangular strip with varying hues, which recorded the score from 0 to 10. A higher score indicated higher pain intensity.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (pre-dose); 15 and 30 min, 1, 2, 4, 6, 11, and 15 h post-dose on Day 1; and at end of study (EOT, Day 2)/early withdrawal (EW)

| End point values | Safety Analysis Population | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 44 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=44) | 3.85 (± 2.049) | | | |
| 15 min (n=44) | 3.3 (± 2.467) | | | |
| 30 min (n=44) | 2.45 (± 2.061) | | | |
| 1 h (n=44) | 2.14 (± 1.839) | | | |
| 2h (n=43) | 1.82 (± 1.823) | | | |
| 4h (n=42) | 2.37 (± 1.976) | | | |
| 6h (n=42) | 2.15 (± 1.553) | | | |
| 11h (n=41) | 2.76 (± 2.367) | | | |
| 15 h (n=41) | 2.41 (± 2.197) | | | |
| EOT/EW (n=44) | 2.3 (± 2.006) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Faces Pain Scale-Revised Score

| | |
|--|---|
| End point title | Faces Pain Scale-Revised Score ^[2] |
| End point description: The FPS-R showed facial images showing different pain levels, with scores ranging from 0 to 10 in the increasing order denoting higher pain intensity. | |
| End point type | Other pre-specified |
| End point timeframe: Baseline (pre-dose); 15 and 30 min, 1, 2, 4, 6, 11, and 15 h post-dose on Day 1; and at EOT/EW | |

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was planned to be reported for the specific arms only.

| End point values | Group 2 (6- <12 years) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=14) | 3.3 (± 2.55) | | | |
| Day 1, 15 min (n=14) | 2.9 (± 2.8) | | | |
| Day 1, 30 min (n=14) | 1.3 (± 1.27) | | | |
| Day 1, 1 h (n=14) | 1.4 (± 1.22) | | | |
| Day 1, 2 h (n=14) | 1 (± 1.3) | | | |
| Day 1, 4 h (n=14) | 1.6 (± 1.95) | | | |
| Day 1, 6 h (n=13) | 0.9 (± 1.55) | | | |
| Day 1, 11 h (n=12) | 2.2 (± 2.48) | | | |
| Day 1, 15 h (n=13) | 1.2 (± 1.74) | | | |
| EOT/EW (n=14) | 1 (± 1.3) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening up to Day 2

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Group 1(12-<18 yrs) |
|-----------------------|---------------------|

Reporting group description:

Group 1(12-<18 yrs) Children with a body weight less than 20 kg will be dosed with a single dose of tapentadol 4 mg/mL OS and children with a body weight of 20 kg or greater will be dosed with a single dose of tapentadol 20 mg/mL OS.

| | |
|-----------------------|--------------------|
| Reporting group title | Group 2(6-<12 yrs) |
|-----------------------|--------------------|

Reporting group description:

Group 2(6-<12 yrs) Children with a body weight less than 20 kg will be dosed with a single dose of tapentadol 4 mg/mL OS and children with a body weight of 20 kg or greater will be dosed with a single dose of tapentadol 20 mg/mL OS.

| Serious adverse events | Group 1(12-<18 yrs) | Group 2(6-<12 yrs) | |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 14 (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 | Group 1(12-<18 yrs) | Group 2(6-<12 yrs) | |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 30 (40.00%) | 8 / 14 (57.14%) | |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Endotracheal intubation complication | | | |

| | | | |
|--|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Post procedural discomfort subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| General disorders and administration site conditions Medical device discomfort subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Hypoaesthesia oral subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 30 (10.00%) 3 | 1 / 14 (7.14%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 30 (20.00%) 7 | 7 / 14 (50.00%) 10 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |

| | | | |
|--|---------------------|---------------------|--|
| Hypoxia subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Swelling face subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 14 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 14 (7.14%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 21 May 2010 | Participants were given approximately 25 milliliter (mL) of water after dosing to help ensure all medication was cleared from the mouth and swallowed and the obligatory intake of 100 mL to 150 mL of water at 1 hour after dosing was removed. |
| 23 February 2011 | The description of safety was moved to precede the efficacy section since PK analyses and safety were 2 primary objectives of the study; Type and use of concomitant rescue analgesic medications were made clear to prevent intolerable pain to participants; Study stopping and participant withdrawal (discontinuation) criteria were modified for tapentadol administration, any potential safety findings, and regulatory requirements to ensure that caution was used to enroll participants; Methods for statistical analyses for safety and pain intensity were revised to include analyses based on concurrent use of analgesic medications; All participants who received study medication but were excluded from the PK analysis were to be included in the safety analysis; Study design was revised to include more details about participant screening, tapentadol administration, and the maximum single oral dose; Additions and modifications were made to inclusion and exclusion criteria to improve the safety for the pediatric population; Safety evaluations were revised to add baseline criteria assessments and type and timing of clinical laboratory tests, 12-lead ECG, and end-of-study physical examination. |
| 12 December 2011 | The main reason for this amendment was to improve enrollment in the study while preserving the original intent and objectives of the study. This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. |
| 24 February 2012 | Modifications were made to the study design and the inclusion and exclusion criteria to facilitate study enrollment while preserving original intent and objectives of the study; The study design was modified to enroll participants pre- or post-operatively; The inclusion criteria were modified to include participants with: dental surgeries or postoperative pain that requires opioid treatment as per the investigator's clinical judgment; Ibuprofen (4-10 mg/kg every 6-8 hours) or naproxen (2.5-10 mg/kg every 8-12 hours) was allowed as supplemental analgesic medication; Participants with contraindications to ibuprofen or naproxen, or significant infectious disease were to be excluded from the study; The safety evaluations were modified to include that physical examination and 12-lead ECG will be performed at screening. |
| 02 July 2012 | The primary objective of this amendment was to permit the enrollment of subjects who were ≥ 6 years of age. This was based on a recommendation from a recent Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (IDRAC 137880 [ACPSCP]), which took place in March 2012. A majority (12 or 13) of the Committee members agreed that the dose of a drug for adolescents may be derived using adult data without the need for a dedicated pharmacokinetic study. Furthermore, the extensive clinical and pharmacological experience with tapentadol supports the use of modeling to select a dose for testing in subjects who are ≥ 6 years of age. This amendment also allowed for the use of any nonsteroidal anti-inflammatory drug (NSAID) for supplemental analgesic medication in the event of persistent pain, instead of limiting the permitted NSAIDs to just ibuprofen and naproxen. This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported