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)	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	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
Investigational medicinal product code	CG5503/R331333
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Dosage and administration details:

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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

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.

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

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