SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	NUCYNTA® (tapentadol) Oral Solution
Name of Active Ingredient(s)	R331333 (tapentadol hydrochloride)

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Status: Approved

Date: 19 February 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: R331333PAI2005 (KF5503/59)

Title of Study: 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

NCT No.: NCT01134536

Clinical Registry No.: CR016891

Principal Investigator: Julia C. Finkel, MD, Director of Research, Division of Anesthesiology and Pain Medicine, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010, USA

Study Center(s): The study was conducted at 34 sites in Canada (3 sites), France (2 sites), Spain (5 sites), and the United States (US) (24 sites). Two sites in France were evaluated but no subjects were enrolled.

Publication (Reference): None

Study Period: 12 October 2011 to 23 March 2013 (Clinical Study Completion Date), 05 September 2013 (Administrative Study Completion Date). Database Lock: 21 November 2013

Phase of Development: 2

Objectives: The primary objective of this study was to evaluate the pharmacokinetic (PK) 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 between 6 years to <18 years after scheduled surgical procedures that routinely produce acute, moderate to severe postsurgical pain.

In addition, the safety and tolerability of tapentadol OS was evaluated and the measurement of pain intensity was explored.

Methodology: This was a multicenter, open-label, single-dose study that evaluated the PK, safety, and tolerability of tapentadol 1 mg/kg in 40 children and adolescents aged 6 years to <18 years with a maximum body weight of 85 kg and body mass index (BMI) <95th percentile. Each eligible subject who entered the study received a single oral dose of tapentadol 1 mg/kg after a scheduled surgical procedure that routinely produce acute, moderate to severe postsurgical pain. The study consisted of a screening phase (≤30 days, including the pre- and postoperative evaluations, the surgical procedure and its postrecovery period), a treatment phase (Day 1), and end-of-treatment phase assessments upon

completion of the 15-hour postdose evaluation. All subjects underwent 15-hour postdose evaluations with PK blood sampling at predefined timepoints. Safety assessment was based on adverse events (AEs), clinical laboratory tests, vital signs measurements, and physical and electrocardiogram (ECG) findings. Pain intensity was measured using the McGrath Color Analog Scale (CAS) for subjects aged 6 to <18 years of age and using Faces Pain Scale Revised (FPS-R) for subjects aged 6 to <12 years of age.

Neuroleptics, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) were prohibited within 14 days of tapentadol administration and during the study. Sedatives were not allowed unless used during surgery.

Number of Subjects (planned and analyzed): Planned: A total of 40 children were planned to be enrolled into the study and receive tapentadol. All subjects who received a dose of tapentadol were included in the safety analysis set. Analyzed: A total of 44 subjects were enrolled and received a dose of tapentadol and were included in the safety and tolerability analysis. Of the 44 subjects, 30 subjects were 12 to <18 years of age (Group 1) and 14 subjects were 6 to <12 years of age (Group 2).

Diagnosis and Main Criteria for Inclusion: Girls and boys between 6 years to <18 years of age with a maximum body weight of 85 kg and BMI <95th percentile, who had a postoperative pain intensity score ≥4 on the McGrath CAS, or had a pain level that required opioid treatment as per investigator's clinical judgment.

Test Product, Dose and Mode of Administration, Batch No.: Tapentadol was supplied for this study as oral solutions of 4.66 mg tapentadol hydrochloride per mL (containing a 4 mg/mL tapentadol base) (Batch No: Expiry Date. 10B10/F041: 28 February 2013, CGZS005/F041: 28 February 2013, and 12G23/F041: 31 July 2015) or 23.3 mg tapentadol HCl per mL (containing 20 mg/mL tapentadol base) (Batch No: Expiry Date. 10B10/F038: 28 February 2013, CGZS004/F038: 28 February 2013, 12G30/F038: 31 July 2015), and the following excipients: citric acid monohydrate, sucralose, raspberry flavor, sodium benzoate (only the 4-mg/mL solution), sodium hydroxide (only the 20-mg/mL solution) and purified water. Tapentadol was administered as a single oral dose.

Reference Therapy, Dose and Mode of Administration, Batch No.: None.

Duration of Treatment: The total study duration, including the screening phase, was up to 32 days.

Criteria for Evaluation:

Pharmacokinetics: Serum concentrations of tapentadol and its major metabolite tapentadol-O-glucuronide were measured for each subject during the 15-hour postdose evaluation period. A 2-mL blood sample was drawn at each timepoint from each subject. Initially, 8 PK samples were to be collected at predetermined timepoints after tapentadol administration from subjects who were 12 to ≤18 years of age and 4 PK samples were to be collected during predetermined intervals from subjects who were 6 to less than 12 years of age. Following a protocol amendment, 4 PK samples were collected during predetermined intervals from all subjects who were enrolled in the study.

Safety: Safety evaluations were based upon the incidence, intensity, and relationship with tapentadol of AEs reported throughout the study, and on changes in vital signs measurements, physical examinations, 12-lead 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.

Assessments of Pain: After the surgery, pain intensity was assessed as per standard-of-care for all the subjects. Pain intensity was assessed for all the subjects by using the McGrath CAS at different timepoints during the treatment and end-of-study phases. An additional pain intensity assessment with the FPS-R was performed in children aged between 6 years to <12 years immediately after the McGrath CAS (less than 2-minute interval). Pain assessments were performed immediately before PK blood sampling and any administration of supplemental analgesic medication.

Statistical Methods:

Sample Size: Based on previous population PK analyses in adults, the study was powered to target a 95% confidence interval (CI) within 71% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for tapentadol in each age group. The sample size was chosen to limit the exposure in pediatric subjects while providing sufficient data to characterize primary PK parameters (eg, CL/F and V2/F) in the studied age range with a population PK modeling approach.

Pharmacokinetics: The concentration-time data of tapentadol and metabolite tapentadol-O-glucuronide were summarized using descriptive methods. In addition, the serum tapentadol and tapentadol-O-glucuronide concentration-time data will be subjected to population PK analysis using non-linear mixed effects modeling. The influence of various demographics such as age and body size (eg, total body weight) on key model parameters (eg, CL/F and V2/F) will be evaluated. The results of population PK analyses will be provided in a separate report.

Safety: All enrolled subjects who received a dose of tapentadol were included in the safety analysis. The analyses included the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to tapentadol discontinuation, as well as the evaluation of laboratory tests, vital signs, physical examination and 12-lead ECGs. The evaluations were summarized by descriptive statistics for each timepoint and the change from baseline (predose) at each timepoint.

Assessments of Pain: All analyses of pain were based on the set of subjects who received tapentadol. For FPS-R, a shift from baseline (predose) table was presented for all scheduled post-treatment timepoints in pre- versus post-treatment cross tabulations. For children aged 6 years to <12 years, scores of both the CAS and the FPS-R were listed per timepoint. Pain Intensity Difference (PID) was derived as the change of pain intensity scores at time 't' from the baseline pain intensity score. Dose and time to intake of supplemental analgesic medication were also analyzed.

RESULTS:

STUDY POPULATION:

A total of 44 subjects (20 males and 24 females) were enrolled and received a dose of tapentadol. The majority of subjects were white (84.1%) with a mean age of 13.0 years. Thirty-eight (86.4%) of the 44 subjects completed the study and 6 (13.6%) subjects were withdrawn (discontinued) from the study. The most common reason for discontinuation was the subject meeting the protocol-defined exclusion criteria of 'vomiting within first 3 hours of tapentadol administration' (n=5). Four subjects reported major protocol deviations during the study (not meeting inclusion/exclusion criteria and missed PK sample draws).

ASSESSMENT OF PAIN RESULTS:

McGrath Color Analog Scale: All 44 subjects had pain assessments performed using McGrath CAS at specified timepoints in the study. Overall, the mean change in the pain intensity scores, post study agent administration, from baseline to the end of the study demonstrated a decrease (improvement) at all timepoints. At baseline, the mean pain intensity score was 3.8. The mean pain intensity scores at postdose ranged from 3.3 (at Day 1, 15 minutes postdose) to 1.8 (at Day 1, 2 hours postdose). The maximum mean change in pain intensity score from baseline was 2.0. At the end of the study, the mean pain intensity score decreased to 2.3 with a mean change of 1.55 from baseline. Similar observations were seen for subjects by age groups in Group 1 and Group 2.

Faces Pain Scale-Revised: The FPS-R pain intensity assessment (based on facial images showing different pain levels) was performed for the 14 subjects in Group 2 (6 to <12 years of age) at specified timepoints in the study. All 14 subjects showed a decrease from baseline in pain intensity scores at all timepoints with a maximum mean decrease of 2.5 at Day 1, 6 hours postdose. At the end of the study, the mean pain intensity score improved to 1.0 (range: 0-4) with a mean change of 2.3 from baseline (mean

score: 3.3). At the end of the study, 13 of 14 subjects had scores ranging from 0 to 2 on FPS-R compared to 7 subjects at baseline.

Intake of Supplemental Analgesic Medication: Overall, 32 (72.7%) of the 44 subjects received supplemental postoperative analgesic medications during the 15-hour postdose evaluation period. Ibuprofen (or naproxen) was the most frequently (45.5%) administered analgesic medication followed by opioids (36.4%), opioid in addition to acetaminophen/paracetamol or ibuprofen or naproxen (29.5%), and acetaminophen/paracetamol (27.3%). Overall, among subjects who received supplemental analgesic medications, 50% of them received supplemental analgesic medications at least twice (median value =2; range: 1-21 times) during the study for persistent pain. The median time to first intake of any supplemental analgesic medication after tapentadol administration was approximately 5 hours and varied as follows: ibuprofen (or naproxen) =6.3 hours, opioids =4.1 hours, and acetaminophen/paracetamol =4.3 hours.

PHARMACOKINETIC RESULTS:

Pharmacokinetic data were available from a total of 44 subjects. A summary of the concentrations of tapentadol and tapentadol-O-glucuronide in serum are summarized in the table below. This descriptive analysis included concentrations from all subjects who received tapentadol, with the exception of tapentadol and tapentadol-O-glucuronide concentrations that were considered to be outlying (ie, substantially lower relative to that of other subjects) based on visual inspection of the data. Over the first 12 hours following study agent administration, mean concentrations for tapentadol and tapentadol-O-glucuronide ranged from 6.97 to 59.2 ng/mL and 167 to 1,250 ng/mL, respectively, for those intervals which included more than 1 subject. One subject had serum tapentadol and tapentadol-O-glucuronide concentrations of 66.8 ng/mL and 1840 ng/mL, respectively, at 1.5 to <2 hours postdose. The PK data summarized in the present report will also be analyzed using population methods and reported separately.

Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum Following Single-Dose Administration of Tapentadol to Pediatric Subjects

Tapentadol Concentrations (ng/ mL)			
Interval	**Number of Subjects**	**Mean**	**Standard Deviation**
>5 min to <30 min	10	10.9	13.8
30 min to <45 min	19	39.1	32.4
45 min to <1 h	10	59.2	26.7
1 h to <1.5 h	16	51.5	26.3
1.5 h to <2 h	1	66.8	-
2 h to <3 h	12	47.1	21.9
3 h to <4 h	10	34.4	8.46
4 h to <5 h	17	30.1	13.6
5 h to <6 h	6	26.5	9.39
6 h to <8 h	9	18.0	7.88
8 h to <12 h	22	6.97	3.89
>12 h	22	4.26	2.95
Tapentadol-O-Glucuronide Concentrations (ng/mL)			
Interval	**Number of Subjects**	**Mean**	**Standard Deviation**
>5 min to <30 min	8	203	183
30 min to <45 min	18	834	706
45 min to <1 h	10	1250	460
1 h to <1.5 h	15	1033	441
1.5 h to <2 h	1	1840	-
2 h to <3 h	12	1241	489
3 h to <4 h	10	1110	359
4 h to <5 h	17	769	287

Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum Following Single-Dose Administration of Tapentadol to Pediatric Subjects

5 h to <6 h	6	714	237
6 h to <8 h	9	402	210
8 h to <12 h	22	167	91.8
>12 h	21	93.7	66.9

Note: Intervals in the table represent the time since the dose of tapentadol was administered.

SAFETY RESULTS: Less than half of the subjects enrolled in the study (45.5% [20/44]) experienced at least 1 TEAE, of which 12 subjects (40.0%) belonged to Group 1 and 8 (57.1%) subjects belonged to Group 2. The majority (29.5%; 13/44 subjects) of the TEAEs by system organ class (SOC) were reported in the gastrointestinal disorders SOC. Vomiting (n=13) and nausea (n=4) were the most common TEAEs reported in this study. All other TEAEs belonging to other SOCs were reported as single incidences. All the events were either mild or moderate in severity. The investigator assessed the TEAEs of vomiting, nausea, hypoesthesia oral, pruritus, swelling face, dizziness, headache, and hypoxia as related to tapentadol. There were no deaths, SAEs, or events leading to discontinuation of tapentadol reported in this study. Overall, no treatment-emergent abnormal laboratory results, vital signs, or ECG values were reported as AEs from baseline at predose to end of the study.

Treatment-Emergent Adverse Events by Body System or Organ Class and Dictionary-derived Term
Safety Analysis Set (Study R331333PAI2005)

	Group 1 (12-<18 yrs)	Group 2 (6-<12 yrs)	Overall (6-<18 yrs)
All safety subjects	30	14	44
Subjects with 1 or more AEs	12 (40.0%)	8 (57.1%)	20 (45.5%)
Body System or Organ Class/ Dictionary-Derived Term			
Gastrointestinal disorders	6 (20.0%)	7 (50.0%)	13 (29.5%)
Vomiting	6 (20.0%)	7 (50.0%)	13 (29.5%)
Nausea	3 (10.0%)	1 (7.1%)	4 (9.1%)
Hypoaesthesia oral	1 (3.3%)	0	1 (2.3%)
Abdominal pain upper	0	1 (7.1%)	1 (2.3%)
Skin and subcutaneous tissue disorders	3 (10.0%)	0	3 (6.8%)
Pruritus	1 (3.3%)	0	1 (2.3%)
Rash	1 (3.3%)	0	1 (2.3%)
Swelling face	1 (3.3%)	0	1 (2.3%)
Nervous system disorders	2 (6.7%)	0	2 (4.5%)
Dizziness	1 (3.3%)	0	1 (2.3%)
Headache	1 (3.3%)	0	1 (2.3%)
Respiratory, thoracic and mediastinal disorders	2 (6.7%)	0	2 (4.5%)
Epistaxis	1 (3.3%)	0	1 (2.3%)
Hypoxia	1 (3.3%)	0	1 (2.3%)
General disorders and administration site conditions	1 (3.3%)	1 (7.1%)	2 (4.5%)
Pyrexia	1 (3.3%)	0	1 (2.3%)
Medical device discomfort	0	1 (7.1%)	1 (2.3%)
Injury, poisoning and procedural complications	0	2 (14.3%)	2 (4.5%)
Endotracheal intubation complication	0	1 (7.1%)	1 (2.3%)
Post procedural discomfort	0	1 (7.1%)	1 (2.3%)
Investigations	0	1 (7.1%)	1 (2.3%)
Oxygen saturation decreased	0	1 (7.1%)	1 (2.3%)
Psychiatric disorders	0	1 (7.1%)	1 (2.3%)
Anxiety	0	1 (7.1%)	1 (2.3%)
Renal and urinary disorders	0	1 (7.1%)	1 (2.3%)
Dysuria	0	1 (7.1%)	1 (2.3%)

Treatment-emergent adverse events(TEAEs) are Adverse Events start after tapentadol administration.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 16.0
MedDRA: Medical Dictionary for Regulatory Activities

STUDY LIMITATIONS: This study was too limited ie, single-dose study with allowance of concomitant analgesic medications, to determine the efficacy of tapentadol from the pain intensity measurements for the pediatric population under study.

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