SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C; in codevelopment with Grünenthal GmbH
Name of Finished Product	To be determined
Name of Active Ingredient(s)	Tapentadol HCl (also known as CG5503 and R331333)

Protocol No.: R33133-PAI-3010 (KF5503/18), CR013567

Title of Study: Open-Label Extension, Single-Arm, Flexible-Dosing, Phase 3 Study With Tapentadol Extended-Release (ER) in Subjects With Moderate to Severe Chronic Pain

Coordinating Investigator: Howard N. Chipman, MD, Medical Director, Journey Research Incorporated, Oldsmar, Florida, United States of America

Publication (Reference): Clinical Registry No.: NCT00487435

Study Period: 04 June 2007 – 29 June 2009; Database lock: 05 November 2009

Phase of Development: Phase 3

Objectives: Primary: characterization of the long-term safety profile of tapentadol ER. Secondary: characterization of: 1) tapentadol ER long-term dose requirements, 2) symptom severity related to constipation, 3) sleep quality, 4) symptoms of withdrawal following discontinuation of treatment, and 5) efficacy based on pain intensity scores (11-point Numerical Rating Scale [NRS], Patient's Global Impression of Change [PGIC], EuroQol-5 Dimension [EQ-5D], and Short Form-36 Health Survey [SF-36].

Methods: This was a single-arm, multiple-administration, open-label extension (OLE), multi-center, safety study of tapentadol ER in subjects with chronic pain who had completed the following studies: PAI-3011/KF23, PAI-3008/KF11, PAI-3007/KF24 (North American sites only), or PAI-3019/KF39. The study consisted of a screening and titration phase (up to 4 weeks), maintenance phase (up to 48 weeks with monthly visits), and a follow-up phase (up to 2 weeks). Eligible subjects from study PAI-3007/KF24 taking tapentadol in an open-label fashion were to continue on the dose they were on and did not need to undergo titration but went directly to the maintenance phase on a monthly visit schedule. All other eligible subjects underwent titration to an optimal therapeutic dose of tapentadol ER. The subjects received tapentadol ER 50 mg twice-daily (b.i.d.), for the first 3 days (6 consecutive doses). Thereafter, increases in the dose were allowed in increments of tapentadol ER 50 mg b.i.d. to achieve a stable optimal dose (i.e., the dose that provided meaningful improvement in pain with acceptable side effects in the subject's perception). During the maintenance phase, subjects were to continue their study drug intake for 48 weeks. Dose increases in increments of tapentadol ER 50 mg b.i.d. were allowed every 3 days, and decreases in the dose using the same increments were allowed at any time. The maximum (minimum) tapentadol ER doses allowed were 250 mg (100 mg) b.i.d. A follow-up visit and a follow-up telephone call (adverse events [AEs] recording only) occurred within 4 days and 10 to 14 days after last study drug intake, respectively. Paracetamol/acetaminophen 2 × 500 mg daily was permitted during the study for a maximum of 7 consecutive days and no more than 14 days out of 30 days.

Number of Subjects (planned and analyzed): The total projected number of subjects eligible for entering the OLE study was expected to be around 1,082. A total of 1,371 subjects were eligible to enter the OLE study. The safety analysis set included 1,154 subjects (a subset of 1,128 subjects were analyzed for PK) and 1,149 subjects were included in the intent-to-treat (ITT) analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were men and non-pregnant, non-lactating women, at least 18 years old, with chronic low back pain or chronic pain due to osteoarthritis of the knee or hip.

Test Product, Dose and Mode of Administration, Batch No.: Tapentadol extended-release oral tablets in doses of 50 mg (Lot Nos.: PD2347, PD2555, PD2558, PD2564, PD2567, PD2711), 100 mg (Lot Nos.: PD2350, PD2440, PD2576, PD2573, PD2281, PD2570, PD2579, PD2717), 150 mg (Lot Nos.: PD2356, PD2449, PD2585, PD2582, PD2723, PD2720), 200 mg (Lot Nos.: PD2365, PD2452, PD2455, PD2588, PD2591, PD2729, PD2726), and 250 mg (Lot Nos.: PD2368, PD2594, PD2458, PD2461, PD2732) were administered b.i.d., in the morning and evening.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The active treatment period of the study was expected to last for 1 year.

Criteria for Evaluation:

Efficacy: Efficacy was assessed by pain intensity scores with an 11-point NRS, PGIC scale, EQ-5D and SF-36 scores, and need for concomitant medication.

Safety: Safety assessment consisted of AE reporting, clinical laboratory tests, vital sign measurements (pulse rate, respiratory rate, and blood pressure), physical examinations, electrocardiogram (ECG), Patient Assessment of Constipation Symptoms (PAC-SYM), Sleep Questionnaire (SQ), and opiate withdrawal using the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS).

Pharmacokinetics: Blood samples were collected at specified visits.

Statistical Methods: All subjects who enrolled in the current study and received at least 1 dose of study drug were included in the safety analysis set. One subject was enrolled in the study twice under 2 different subject ID numbers; only data from the first enrolment were included in the safety analysis set. The ITT analysis set had the same definition as the safety analysis set but excluded the 5 subjects treated at Site 001089 which had major audit findings identified prior to database lock.

All analysis summaries were displayed for all subjects in the safety and ITT analysis sets, regardless of the doses individual subjects received during the OLE study. Subjects were grouped according to the previous treatment received during the parent study (i.e., placebo ≤15 wks, tapentadol ≤15 wks, oxycodone 15 wks, tapentadol 1 yr, oxycodone 1 yr; referred to as prior randomization group). Summary tables included results from only the current OLE study, and all summary displays showed data for each prior randomization group and for the All Tapentadol ER group. Inclusion of data, except medical history, from the parent studies was outside of the scope of the clinical study report for the current OLE study. Statistical analyses consisted of descriptive summaries of safety and efficacy data. No formal hypothesis testing or inferential analysis was performed. Within subject comparisons could be made with the subject itself as comparator by examining the data over time using the descriptive statistics. Summaries for continuous variables (descriptive statistics) included mean, standard deviation, median, N, and range. Summaries for categorical variables included frequency counts and percentage of subjects.

Pharmacokinetics: Results of the population pharmacokinetic analyses and the relationship between pharmacokinetics and selected efficacy and safety parameters will be reported separately.

RESULTS:

STUDY DRUG EXPOSURE:

A total of 1,154 subjects were enrolled and received at least 1 dose of tapentadol ER (safety analysis set) following short-term treatment (≤15 weeks) with placebo (n=303), tapentadol ER (n=358), or oxycodone (n=199) or long-term (1 year) treatment with tapentadol ER (n=249) or oxycodone (n=45) in the parent studies. Approximately 58% of subjects were female. The majority of subjects were white (78.9%) and under 65 years of age (82.7%).

More than one-half (60.5%) of subjects in the safety analysis set completed the treatment period. The most common reasons for treatment discontinuation were AEs (13.0%) and subject choice (10.6%). The treatment discontinuation rate was lower for subjects who received 1 year of prior treatment with tapentadol (24.1%) than for those who received 1 year of prior treatment with oxycodone (31.1%) or short-term treatment with tapentadol (41.5%), oxycodone (42.9%), or placebo (48.8%).

The median duration of treatment was 339 days (48.4 weeks) across all treated subjects, and 819 (70.9%) and 195 (16.9%) subjects who took study drug for at least 6 or 12 months, respectively. The mean total daily dose of tapentadol ER was 368.2 mg. The mean total daily dose increased until approximately 4 weeks and then was maintained until the end of the study (at approximately 400 mg). Subjects who required titration had to be titrated to the dose that provided optimal therapeutic benefit during the first 4 weeks of the current study.

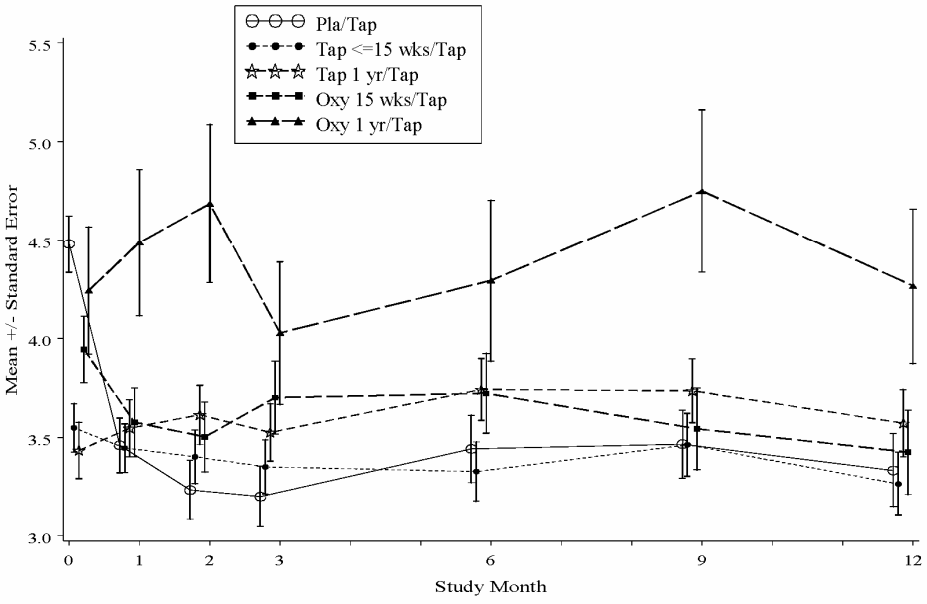
For each individual study, the longest number of consecutive days at the high dose (defined as ≥400 mg/day) was calculated. The mean number of days for the longest number of consecutive days at the high dose with no dose change was 146 days.

EFFICACY RESULTS:

Pain Intensity

Pain intensity was measured at each time point using an 11-point NRS from 0 to 10, 0 representing 'no pain' and 10 representing 'pain as bad as you can imagine'. Pain intensity scores remained stable or improved slightly over the treatment period (Figure 1), with subjects who received placebo in the parent study showing, on average, the largest decrease in pain intensity scores during tapentadol ER treatment in the current OLE study. By Week 4 (Month 1), mean pain intensity scores in the Pla/Tap group were similar to those in the other prior randomization groups. Across all treated subjects, the mean baseline pain intensity score was 3.87 and was 3.65 at the end of the treatment period.

Figure 1: Pain Intensity Score over Time based on NRS Scores by Prior Randomization Group (ITT Analysis Set)



N							
Pla/Tap	303	291	231	219	199	178	159
Tap <=15 wks/Tap	357	349	303	290	259	235	215
Tap 1 yr/Tap	246	243	234	230	222	205	192
Oxy 15 wks/Tap	198	181	155	151	134	125	115
Oxy 1 yr/Tap	45	41	35	35	34	32	30

Tapentadol ER = Tapentadol PR.

Tolerance
The stability of both the modal and average doses along with steadiness of the analgesic scores throughout the study supports that there was no tolerance to the tested dose ranges in the 12-month duration of the study for tapentadol ER in this population.

Patient's Global Impression of Change (PGIC)
Overall, subjects had a positive Global Impression of Change at the end of the study. Approximately two-thirds of subjects (61.4%) reported a change of 'Very Much Improved' or 'Much Improved' at end point.

Additional Patient-Reported Outcomes
SF 36 Health Survey: Improvements were observed over all SF-36 dimensions of physical, social and mental well being, as well as for the physical and mental component summary scores parameters.

EuroQoL 5 Dimension Questionnaire: Mean changes from baseline over time were small for all 5 dimensions.

PHARMACOKINETIC RESULTS: Results of the population pharmacokinetic analyses and the relationship between pharmacokinetics and selected efficacy and safety parameters will be reported separately. Serum tapentadol concentrations from 3,694 samples are included in the bioanalytical report attached to this report.

SAFETY RESULTS: Overall, tapentadol ER was well tolerated across the studied dose range of 100 to 250 mg b.i.d. for up to 1 year in this OLE study in adult subjects with chronic pain. The overall safety profile in this OLE study was very similar to that established in the previous studies with tapentadol ER and IR. There were no unexpected safety findings among AEs, laboratory values, vital sign measurements, or ECG recordings.

The lowest incidence of TEAEs and discontinuations due to TEAEs was observed in subjects who had previously been exposed to tapentadol ER in the parent study, and the highest occurred in subjects previously on placebo treatment (Table 1).

Table 1: Overall Safety Profile
(Safety Analysis Set)

	Pla/Tap (N=303) n (%)	Tap ≤15 wks/Tap (N=358) n (%)	Tap 1 yr/Tap (N=249) n (%)	Oxy 15 wks/Tap (N=199) n (%)	Oxy 1 yr/Tap (N=45) n (%)	All Tap ER (N=1154) n (%)
Deaths	1 (0.3)	1 (0.3)	0	0	1 (2.2)	3 (0.3)
SAEs	23 (7.6)	27 (7.5)	22 (8.8)	9 (4.5)	3 (6.7)	84 (7.3)
Discontinuation for TEAE	53 (17.5)	39 (10.9)	14 (5.6)	26 (13.1)	7 (15.6)	139 (12.0)
TEAE	256 (84.5)	278 (77.7)	187 (75.1)	152 (76.4)	34 (75.6)	907 (78.6)

Percentages are calculated with the number of subjects in each group as denominator.
Tapentadol ER = Tapentadol PR.
Note: The treatment groups indicate the treatment in the parent study/treatment of the OLE study or all subjects in the OLE study = All Tap ER

There were 3 subject deaths during this 1-year study, 2 of which were cardiac related in subjects with a history of cardiovascular disease and 1 completed suicide that occurred 3 days after study discontinuation due to family issues in a subject with a history of chronic depression and current depression symptoms.

Serious adverse events (SAEs) were reported by 84 subjects (7.3%) overall, and no SAE was reported by more than 3 (0.3%) subjects except for osteoarthritis (0.6%). Most SAEs were assessed by the investigator as unrelated or unlikely related to study treatment; the incidence of treatment-related SAEs was very low (<1%).

A total of 139 subjects (12.0%) had TEAEs that led to study discontinuation. The most common TEAEs that led to study discontinuation were nausea and dizziness.

There were few potentially clinically important findings in laboratory, vital signs, or ECG values based on predefined criteria. The percentage of all treated subjects who had a normal baseline value and at least 1 post baseline value that met PCI criteria was <1% for all hematology, chemistry and urinalysis analytes, and <3% for pulse rate, BP, and respiration rate, and all ECG interval parameters.

Four (4) subjects (0.3%) who had a QTc interval value of <500 ms at baseline experienced a QTc interval prolongation of ≥500 ms while on tapentadol ER. Three of these subjects had a cardiac-related medical history. The QTc interval prolongation did not suggest a causal relationship to the administration of tapentadol ER for these subjects. For the remaining subject, the QTc interval prolongation occurred on the same day as a TEAE of myocardial ischemia.

Assessment of withdrawal symptoms, using the COWS, demonstrated that most of the 705 subjects (≈90%) who did not take an opioid at the time of the evaluation during the follow-up phase did not experience clinical symptoms of opioid withdrawal after stopping tapentadol ER treatment, and <1% had moderate withdrawal symptoms. No dose response was apparent for COWS responses, with most subjects within each modal dose category experiencing no withdrawal after stopping tapentadol ER. The subject-completed SOWS questionnaire also indicated a very low incidence of withdrawal after discontinuation of tapentadol ER. This confirms low physical dependence for tapentadol ER treatment with extended treatment.

Overall, no noteworthy changes were observed in the 4 items of the Sleep Questionnaire.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS: Long-term therapy with tapentadol ER at a dose range of 100 to 250 mg b.i.d. was well tolerated in subjects with moderate to severe chronic pain. In this OLE study, the mean TDD for tapentadol ER remained stable over the up to 1-year-long treatment period. No new clinically important safety signals were evident during long-term treatment with tapentadol ER relative to results of previous studies with tapentadol ER or tapentadol IR.

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