SYNOPSIS

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Name of Sponsor/Company	Grünenthal GmbH / Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	not available
Name of Active Ingredient(s)	Tapentadol

Protocol No.: R331333-PAI-3001 (KF5503/31) (CR011221)

Title of Study: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Doses of Tapentadol Immediate-Release Formulation in the Treatment of Acute Pain From Total Hip Replacement Surgery Followed by a Voluntary Open-Label Extension

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Publication (Reference): none

Study Period: 21 September 2006 - 22 December 2007

The study was terminated by the Sponsor for slow recruitment and high discontinuation rates.

Phase of Development: 3

Objectives: The primary objective of this study was to determine the efficacy of tapentadol immediate release (IR) using the sum of pain intensity difference (SPID) over 48 hours compared with placebo and to assess the safety and tolerability of multiple doses of tapentadol IR over the double-blind treatment period in subjects with acute pain following primary unilateral total hip replacement surgery.

The secondary objectives included the evaluation of the following parameters across treatment regimens: a) comparison of the effect of tapentadol IR on the time to the first rescue pain medication use during the double-blind treatment period, b) evaluation of the effect of tapentadol IR versus placebo using the distribution of responder rates at each time point (i.e., at 12, 24, 48, and 72 hours) during the double-blind treatment period, c) evaluation of the efficacy of tapentadol IR by examining the total effect on pain intensity and pain relief over the 72-hour double-blind treatment period, d) assessment of the Patient Global Impression of Change (PGIC) at the end of the double-blind treatment period, e) evaluation of the adverse event rates (especially for nausea and vomiting) across treatment groups in the double-blind treatment period, f) evaluation of tapentadol IR pharmacokinetics using the population pharmacokinetic approach in this study population (population pharmacokinetics will not be analyzed because the study was terminated), g) evaluation of the safety profile and the use of tapentadol IR beyond 3 days in subjects who participated in the open-label extension period, and h) exploration of the efficacy of oxycodone IR in comparison with tapentadol IR and with placebo.

Methods: This was a multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled study with a voluntary open-label extension period to evaluate the efficacy and safety of multiple oral doses of tapentadol IR in providing pain relief in subjects with postoperative pain following total hip replacement. The study included a screening period (Days –28 through -2), a surgical period (Day –1), a qualification period (Day 1, starting at the termination of postsurgical patient-controlled analgesia and ending at qualification/randomization or after 6 hours), a double-blind treatment period (Days 1 to 3; 72 hours following randomization), and an open-label extension period (Days 4 to ≤13 with a safety follow-up 13 to 18 days post-surgery). Subjects qualified to enter the study when they reached a pain intensity score ≥4 on an 11-point numerical rating scale within 6 hours

of the termination of the postsurgical patient-controlled analgesia. Pharmacokinetics, pharmacogenomics, efficacy, and safety were assessed during the double-blind treatment period. Subjects who completed the double-blind treatment period had the option to continue in the open-label extension period, during which time only safety was assessed.

Qualified subjects were randomly assigned to 1 of the following treatment groups: placebo, tapentadol IR 50 mg, tapentadol IR 75 mg, tapentadol IR 100 mg, or oxycodone HCl IR 10 mg. Subjects were administered a single oral dose of assigned study drug every 4 to 6 hours. On Day 1 only, subjects were permitted to take their second dose of study drug as soon as 1 hour (and not later than 6 hours) after the first dose.

During the open-label treatment period, 1 or 2 capsules (i.e., 50 or 100 mg of tapentadol IR) were to be taken every 4 to 6 hours, as needed for pain.

During the study, Site 011006 was closed due to site misconduct in which data irregularities were observed.

Number of Subjects (planned and analyzed): Planned: 1,100 (220/group); randomized: 365 subjects total; analyzed for efficacy (intent-to-treat analysis set [ITT]): 330 subjects, (per-protocol set): 260 subjects; analyzed for safety during the double-blind treatment period (Safety set): 365 subjects, (Safety – Exclude 011006 Site): 330 subjects; analyzed for safety during the open-label extension period (OL Safety): 104 subjects, (OL Safety – Exclude 011006 Site): 78 subjects; analyzed for pharmacokinetics: 574 samples.

Diagnosis and Main Criteria for Inclusion: Study subjects were men and women at least 18 and no more than 85 years of age, inclusive, with moderate to severe pain (≥4 on the 11-point NRS) within 6 hours after termination of postoperative patient-controlled analgesia following total hip replacement surgery.

Test Product, Dose and Mode of Administration, Batch No.: Double-blind treatment period: overencapsulated tablets containing 50 mg (batch numbers: PD2025, PD2085, PD2230, PD2341, and PD2542), 75 mg (batch numbers: PD2026, PD2297, PD2300, and PD2543), or 100 mg (batch numbers: PD2027, PD2120, and PD2544) tapentadol IR. Capsules were orally administered. The HCl salt form of the drug substance was used, but the doses are expressed as the free base.

Open-label extension period: 50-mg tablets of tapentadol IR (batch numbers: PD2021 and PD2537). Tablets were to be taken orally in doses of 1 or 2 tablets (i.e., 50 or 100 mg of tapentadol IR).

Reference Therapy, Dose and Mode of Administration, Batch No.: Double-blind treatment period: Capsules matching those for tapentadol IR containing placebo (batch numbers: PD1959, PD1994, and PD2319) or oxycodone HCl IR 10 mg (batch numbers PD2198, PD2228, and PD2072). Capsules were orally administered. No reference therapy was administered during the open-label extension period.

Duration of Treatment: Double-blind study drug was administered as a single capsule, once every 4 to 6 hours over the 72 hours following randomization. On Day 1 only, subjects were permitted to take their second dose of study drug as soon as 1 hour (and no later than 6 hours) after the first dose.

Open-label study drug was to be taken every 4 to 6 hours, as needed for pain, over the 9 days following the double-blind treatment period.

Criteria for Evaluation: Pharmacokinetics: Venous blood samples were collected via an indwelling catheter at approximately 1 and 3 hours after the first dose of study drug on Day 1 or whenever possible. On Day 2, samples were collected before (predose) and approximately 2 hours after the third dose of study drug, or whenever possible, to determine tapentadol and oxycodone concentrations. Samples from placebo-treated subjects were not analyzed. The quantification of 2 oxycodone metabolites (noroxycodone and oxymorphone) was performed.

Pharmacodynamics: No pharmacodynamics analysis was performed.

Efficacy: SPID at 48 hours was the primary efficacy variable (i.e., the cumulative effects of drug exposure on pain intensity over the first 48 hours of the 72-hour double-blind treatment period). Subjects performed pain intensity and pain relief assessments. The PGIC was assessed at the end of the double-blind treatment period.

Safety: Safety and tolerability assessments were based on adverse events and changes in clinical laboratory tests, vital signs (pulse rate, temperature, blood pressure, and respiratory rate), pulse oximetry (SpO_2), 12-lead electrocardiograms, and physical examination.

Pharmacokinetic/Pharmacodynamic Relationships: No pharmacokinetic/pharmacodynamic analysis was performed.

Pharmacogenomics: Blood to obtain DNA samples was taken after the first study drug administration to analyze genes associated with tapentadol or pain that may influence pharmacokinetics, efficacy, safety, or tolerability.

Statistical Methods: Sample Size Determination: The desired number of subjects per treatment group (220 subjects) was based on an effect size of 0.35 for the primary efficacy endpoint, which was considered clinically and statistically significant compared with placebo for the tapentadol IR 50 mg dose in subjects undergoing total hip replacement surgery. Assuming the standard effect size discussed above, using the Bonferroni adjustment, it was estimated that approximately 220 subjects for each treatment group would provide 90% power to show that at least 1 tapentadol IR treatment group was statistically different from placebo at an overall alpha level of 0.05.

Pharmacokinetics: Serum concentrations as a function of time were explored for tapentadol and for oxycodone and its metabolites, noroxycodone and oxymorphone.

Efficacy: Analysis Planned - The primary efficacy analysis on the primary endpoint ($SPID_{48}$ with last observation carried forward [LOCF]) was an analysis of covariance (ANCOVA) with the factors of treatment, pooled center, and baseline pain intensity as covariate. All pair-wise treatment differences were estimated based on the least-square means of the difference (LSD). The Hochberg procedure was used to adjust the p-values for multiple comparisons for all tapentadol IR groups compared with the placebo group. All other secondary variables were analyzed separately without multiple-comparison adjustment. Sensitivity analyses were performed with various imputation schemes (baseline observation carried forward [BOCF] and worst observation carried forward [WOCF]) to evaluate the robustness of the observed treatment effects on the primary efficacy endpoint. Additional analyses included analyses by subgroup (sex, racial/ethnic group, age group, baseline pain intensity, and early second dosing with study drug) and analyses versus oxycodone.

Analysis Performed - Because the Sponsor terminated the study and the planned sample size was not reached in any treatment group, the utility of the efficacy analyses is limited. Therefore, only the analysis of the primary efficacy variable ($SPID_{48}$), considered as being of exploratory in nature (exploratory analysis), was presented.

The ITT analysis set was used for the efficacy analyses and included all randomized subjects who received at least 1 dose of double-blind study drug and had a baseline pain assessment. Data from Site 011006 in Canada was excluded from the ITT analysis set.

Safety: Descriptive statistics and frequency analysis (percentage of subjects) were used to assess safety variables, including adverse events, laboratory results, vital signs, and electrocardiogram assessments. Change in response from baseline for each treatment group was assessed.

For the double-blind treatment period, the safety analysis set (named: Safety) was defined as all randomized subjects who received at least 1 dose of study drug. An additional safety analysis set (named: Safety – Exclude 011006 Site) was defined as all subjects in the Safety analysis set, with the exclusion of subjects from Site 011006.

For the open-label extension period, the safety analysis set (named: OL Safety) was defined as all subjects who received at least 1 dose of open-label study drug. An additional safety analysis set (named: OL Safety – Exclude 011006 Site) was defined as all subjects in the Safety analysis set, with the exclusion of subjects from Site 011006, who received at least 1 dose of open-label study drug.

Pharmacokinetic/Pharmacodynamic Relationships: No pharmacokinetic/pharmacodynamic analysis was performed.

Pharmacogenomics: No results of pharmacogenomics analyses or formal statistical tests are reported in this clinical study report.

RESULTS:

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: Most demographic and baseline characteristics were balanced across the treatment groups in the double-blind treatment period. Most subjects in the study were White (93%), and 54% of subjects were women. The average age of the study population was 63 years. In total, 79% of subjects were categorized as having moderate baseline pain intensity (NRS pain intensity ≥4 and <6); the overall mean score was 4.8 Twenty-five percent to 32% of subjects reported prior opioid experience at screening defined as any opioid analgesic used within 30 days before screening. The median BMI was 28.5 (16;62) kg/m².

Of the 156 subjects who completed the double-blind period, 109 (70%) subjects entered the open-label period. In the open-label period, most of the subjects were White (97%), and 53% of the subjects were women. The average age of subjects was 64.2 years. The median (range) BMI was 29.0 (19;44) kg/m².

The mean total daily exposure (mg) in each of the active-treatment groups was similar over the 3 day double-blind period. With the exception of the number of subjects who discontinued treatment and therefore would have taken 3 or fewer doses per day, the majority of subjects in all treatment groups took between 4 to 6 doses of study drug per day corresponding to dosing every 4 to 6 hours.

During the open-label treatment period, the percentage of subjects taking any dose of tapentadol IR (50 mg or 100 mg) decreased from a peak of 93% (97/104) on Day 5 of the study (i.e., the second day of the open-label period) to 61% (63/104) on Day 12 (Day 8 of the open-label period). The average number of days that subjects took study drug was 7.3 (standard deviation of 2.51) days. The mean daily dose ranged between a maximum of 336.6 mg on Day 6 with the majority of subject ending their exposure to the study drug by Day 12.

PHARMACOKINETICS: Upon dose-normalization to 75 mg, an approximate dose-proportional increase was observed in serum concentration of tapentadol. High intersubject variability (%CV) was observed for measured tapentadol, oxycodone, noroxycodone, and oxymorphone serum concentrations for samples taken 1 hour after study drug intake on Day 1. High intersubject variability in serum concentrations for the 1 hour post-dose sample on Day 1 was not unexpected owing to the permitted variation in blood sampling times from 0.5 hour to 1.5 hour. The observed variabilities were consistent with previous pharmacokinetic analyses of tapentadol and oxycodone. The serum concentration ratios of oxycodone metabolites to oxycodone (i.e., metabolite to parent ratio) for noroxycodone and oxymorphone were in the expected range, and the accumulation of both metabolites were slightly higher than the expected behavior, most likely due to the high subject variability.

PHARMACODYNAMICS: No pharmacodynamics analysis was performed in this study.

EFFICACY RESULTS: Primary efficacy variable: Because the Sponsor terminated the study and the planned sample size was not reached in any treatment group, only the analysis of the primary efficacy variable ($SPID_{48}$) was presented. All tapentadol IR treatment groups, as well as the oxycodone HCl IR 10 mg group, showed a statistically significant improvement in pain on the primary efficacy variable of $SPID_{48}$ compared with placebo using the LOCF imputation for subjects who discontinued from the study.

SAFETY RESULTS: The overall percentage of subjects with treatment-emergent adverse events (TEAEs) during the double-blind period was similar in all treatment groups (72% in the placebo group, 74% in the tapentadol IR 50 mg group, 68% in the tapentadol IR 75 mg group, 79% in the tapentadol IR 100 mg group, and 75% in the oxycodone IR 10 mg group). During the double-blind treatment period, the most common TEAEs in the active treatment groups (≥10% in any active-treatment group) were somnolence, dizziness, headache, nausea, constipation, vomiting, dry mouth, confusional state, hallucination visual, pyrexia, body temperature increased, and anaemia. A higher incidence of confusional state and hallucination, visual was observed in subjects with the tapentadol IR 100 mg group (15% and 11%, respectively) compared with the other active-treatment groups (tapentadol IR 50 mg: 8% and 3%; tapentadol IR 75 mg: 6% and 7%; and oxycodone IR 10 mg 3% and 3%, respectively). During the open-label treatment period, the most common TEAEs occurred in a low percentage of subjects and included constipation (13% of all subjects in the open label period), diarrhoea (6%), nausea (8%), and vomiting (5%). Somnolence, dizziness, pyrexia, hallucination visual, confusional state, and anaemia were reported in 3%, 4%, 4%, 2%, 0%, and 2% of subjects during the open-label period, respectively.

There were no deaths at any time during the study. During the double-blind treatment period, 6 subjects reported serious TEAEs (1 subject in the tapentadol IR 50 mg group with supraventricular tachycardia, pulmonary embolism, and deep vein thrombosis, 1 subject in the tapentadol IR 75 mg group with ileus, 3 subjects in the tapentadol IR 100 mg group [1 subject with chronic obstructive pulmonary disease, 1 subject with atrial fibrillation, and 1 subject with lethargy], and 1 subject in the oxycodone IR 10 mg group with confusional state). During the open-label treatment period, 3 subjects had serious TEAEs that included 1 subject with impaired healing, 1 subject with traumatic haematoma, and 1 subject with both anxiety and delirium.

The percentage of subjects with adverse events leading to discontinuation was 3% for placebo, 10% for tapentadol IR 50 mg, 10% for tapentadol IR 75 mg, 20% for tapentadol IR 100 mg, and 7% for oxycodone HCl IR 10 mg groups during the double-blind period. A low percentage of subjects discontinued from the open-label treatment period because of adverse events.

For the double-blind and open-label periods, examination of mean values over time did not reveal clear or consistent patterns for chemistry, hematology, urinalysis, vital signs or ECG. The mean laboratory elevation in lipase could be attributed to an outlying value, which was also documented as a TEAE. Examination of individual abnormal values for vital signs revealed single occurrences and TEAEs in the context of blood pressure and oxygen saturation decrease. In summary, the incidence of such single occurrences of variations was low and there was no apparent dose-related association of mean changes with tapentadol IR administration.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: No pharmacokinetic/ pharmacodynamic analysis was performed for this study.

PHARMACOGENOMICS: Results of the genetic association analyses, if performed in the future, will be reported at that time.

CONCLUSION: Tapentadol IR, in a fixed-dose regimen (50 mg, 75 mg, or 100 mg) administered every 4 to 6 hours, including an early second dose option on the first day, had a safety profile consistent with centrally acting analgesics with mu-opioid agonist activity in subjects with moderate to severe acute pain on the first day following total hip replacement. TEAEs under the SOC Psychiatric Disorders were observed in all active treatment groups (tapentadol IR as well as oxycodone IR). The incidence was higher in subjects treated with tapentadol IR 100 mg compared with oxycodone IR 10 mg, particularly in subjects who were ≥65 years old. The safety profile of tapentadol IR 50 mg or 100 mg administered during the out-patient open-label treatment period was also consistent with centrally acting analgesics with mu-opioid agonist activity.

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