CLINICAL STUDY REPORT SYNOPSIS

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Name of Finished Product	not available	
Name of Active Ingredient(s)	Tapentadol	

Protocol No.: R331333-PAI-3002 (KF5503/33), CR011218

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 CG5503 Immediate Release Formulation in Subjects Awaiting Primary Joint Replacement Surgery for End-Stage Joint Disease

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Publication (Reference): none

Study Period: 24 October 2006 to 22 August 2007	**Phase of Development:** 3

Objectives: The primary objectives of this study were to determine the efficacy of tapentadol immediate release (IR) using the sum of pain intensity difference over 5 days (5-day SPID) compared with placebo and to assess the safety and tolerability of multiple doses of tapentadol IR over the double-blind treatment period in subjects who were eligible for elective primary total or partial joint replacement of the hip or knee due to chronic osteoarthritis.

The secondary objectives included the evaluation of the following parameters across treatment regimens: a) comparison of the effect of tapentadol IR with placebo in time to the first rescue pain medication use during the double-blind treatment period, b) evaluation of the effect of tapentadol IR with the distribution of responder rates based on percent change from baseline in pain intensity for each of the time points (i.e., Days 2, 5, and 10), c) demonstration of the efficacy of tapentadol IR using total pain relief (TOTPAR); the sum of total pain relief and sum of pain intensity difference (SPRID) over 2, 5, and 10 days; and the SPID over 2 and 10 days, d) evaluation of Patient Global Impression of Change (PGIC) of study treatment at the end of the double-blind treatment period, e) evaluation of the adverse event rates across treatment groups (especially nausea and vomiting), f) exploration of sleep quality and bowel movement using questionnaires, g) exploration of the efficacy of oxycodone IR in comparison with tapentadol IR and placebo.

For selected secondary objectives, the statistical analysis plan defined a sequential gate-keeping approach to control the overall Type I error rate using only those tapentadol IR groups that were significantly different from placebo on the primary analysis. If a comparison did not show a significant superiority to oxycodone HCl IR in the adverse event rate comparison or did not demonstrate non-inferiority in 5-day SPID, the subsequent comparisons in the hierarchy were not statistically tested.

- Compare the tapentadol IR 50 mg group with the oxycodone HCl IR 10 mg group in terms of the composite event rate of nausea and vomiting;
- Test the non-inferiority of tapentadol IR 75 mg to oxycodone HCl IR 10 mg using 5-day SPID with a 10% non-inferiority margin;
- Compare the tapentadol IR 75 mg group with the oxycodone HCl IR 10 mg group in terms of the composite event rate of nausea and vomiting;
- Test non-inferiority of tapentadol IR 50 mg to oxycodone HCl IR 10 mg using 5-day SPID with a 10% non-inferiority margin;
- Compare the tapentadol IR 50 mg group with the oxycodone HCl IR 10 mg group in terms of the constipation adverse event rate;
- Compare the tapentadol IR 75 mg group with the oxycodone HCl IR 10 mg group in terms of the constipation adverse event rate;
- Compare treatment effect for the tapentadol IR groups with the placebo group on the time to the first rescue medication use during the double-blind treatment period.

SYNOPSIS (CONTINUED)

Methodology: This was a multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled, outpatient study to evaluate the efficacy and safety of multiple oral doses of tapentadol IR in treating pain in subjects who were candidates for primary total or partial joint replacement surgery for end-stage degenerative joint disease of the hip or knee. The study included a screening period (Days –28 through –8), a run-in period (Days –7 through –1), a double-blind outpatient treatment period (Days 1 through 10), and a follow-up period (Days 11 through 15). During the run-in period, subjects were requested to record pain intensity levels in a diary twice daily for study qualification. To qualify for the study treatment, subjects had to have (1) a mean pain intensity score equal to or greater than 5 on an 11-point (0 to 10) numeric rating scale (NRS; after rounding 4.5 and above to an integer), and (2) a minimum single assessment pain intensity score equal to or greater than 3 on an 11-point (0 to 10) NRS during the last 3 days of pain assessments.

Qualified subjects were randomly assigned to 1 of the following 4 treatment groups: placebo, tapentadol IR 50 mg, tapentadol IR 75 mg (tapentadol IR 50 mg on Day 1 as a titration step and tapentadol IR 75 mg for Days 2 to 10), or oxycodone HCl IR 10 mg. All subjects started their first dose after they arrived home on Day 1. Subsequent doses were to be taken every 4 to 6 hours relative to the previous dose during waking hours. Subjects were instructed to begin diary entries for the double-blind period on the evening of Day 1. Pain assessment entries were to be continued approximately every 12 hours thereafter. During the double-blind treatment period, bowel movement and vomiting questionnaires were to be completed every evening, and a sleep evaluation questionnaire was to be completed at screening, baseline, and the mid-study visit.

Number of Subjects (planned and analyzed): Planned: 624 (156/group); analyzed for efficacy (intent-to-treat [ITT] analysis set): 659 subjects; analyzed for safety (safety set): 666 subjects.

Diagnosis and Main Criteria for Inclusion: Study subjects were men and women at least 18 and no more than 80 years of age who experienced pain from noninflammatory, end-stage degenerative joint disease of the hip or knee and were candidates for primary total or partial joint replacement. Subjects had to have (1) a mean pain intensity score equal to or greater than 5 (after rounding 4.5 and above to an integer), and (2) a minimum single assessment pain intensity score equal to or greater than 3 on an 11-point (0 to 10) NRS during the last 3 days of pain assessments during the run-in period.

Test Product, Dose, and Mode of Administration, Batch No.: Overencapsulated tablets of tapentadol IR 50 mg (batch PD2119) or 75 mg (batches PD2121 and PD2297). Capsules were orally administered. The HCl salt form of the drug substance was used, but the doses are expressed as the free base. The tapentadol IR 75 mg treatment included a titration step of 50 mg tapentadol IR on Day 1 as a single titration step and tapentadol IR 75 mg for Days 2 to 10.

Reference Therapy, Dose, and Mode of Administration, Batch No.: Overencapsulated tablets matching those for tapentadol IR containing placebo (batch PD1994) or oxycodone HCl IR 10 mg (batches PD2198 and PD2118). Capsules were orally administered.

Duration of Treatment: Subjects were provided study treatment on Day 1 during their clinic visit and were instructed to take the first dose that same day when they arrived home. Subsequent doses were to be taken every 4 to 6 hours relative to the previous dose during waking hours.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Pharmacokinetics: No pharmacokinetics analysis was performed.

Pharmacodynamics: No pharmacodynamics analysis was performed.

Efficacy: The 5-day SPID was the primary efficacy variable (i.e., the cumulative effects of drug exposure on pain intensity for Day 1 to Day 5 of the 10-day double-blind treatment period). The secondary efficacy variables were selected to provide a comprehensive assessment of the total effect, duration of effect, and overall response to the proposed dosing regimens. Pain scale variables included: a) SPID at the other time points (Days 2 and 5), and b) TOTPAR and SPRID at each observation time point (Days 2, 5, and 10). Response rates were evaluated as the distribution of responder rates at Days 2, 5, and 10, with response based on the percent change in pain intensity from baseline. Duration of effect was determined based on time to rescue medication use. The PGIC was assessed at the end of the double-blind treatment period. Comparisons of oxycodone HCl IR 10 mg with placebo and with tapentadol IR were also performed.

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

Subjects were asked to complete bowel movement, sleep evaluation, and vomiting questionnaires.

Pharmacokinetic/Pharmacodynamic Relationships: No pharmacokinetics/pharmacodynamics analysis was performed.

Pharmacogenomics: Blood to obtain DNA samples was taken at randomization 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 (156 subjects) was based on an effect size of 0.4, which was considered clinically significant pain relief compared with placebo for the tapentadol IR 50 mg dose in subjects waiting for primary total or partial joint replacement surgery. Assuming the standard effect size mentioned above, and using a Bonferroni adjustment for multiplicity, it was estimated that approximately 156 subjects for each treatment group would provide 90% power to show that at least 1 tapentadol IR dose group was statistically different from placebo at an overall alpha level of 0.05.

Efficacy: The primary efficacy analysis on the primary endpoint (5-day SPID with last observation carried forward [LOCF]) was an analysis of covariance (ANCOVA) with the factors of treatment, pooled center, and baseline pain intensity as covariates. 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 and the placebo group. For time to first rescue medication, comparisons versus placebo were performed if the treatment groups showed significant results in the primary end-point and if the hypothesis test criteria for selected secondary objectives for tapentadol IR versus oxycodone HCl IR were met. If both treatment groups were to be compared for the time to rescue medication, the Hochberg procedure was used to adjust for the multiple comparisons. All other secondary variables were analyzed separately without multiple-comparison adjustment. Exploratory analyses were performed with various imputation schemes (baseline observation carried forward [BOCF], worst observation carried forward [WOCF], and modified LOCF) to evaluate the robustness of the observed treatment effects. Additional analyses included analyses by subgroup (i.e., sex, race, age, and baseline pain intensity) and analyses versus oxycodone HCl IR.

The ITT analysis set was used for the efficacy analyses and included all randomized subjects who received any amount of study drug (i.e., at least one study drug intake following randomization) and had a valid baseline pain assessment.

Safety: Descriptive statistics and frequency analysis (percentage of subjects) were used to assess safety variables, including adverse events, laboratory results, vital signs, and ECG assessments, and data from the bowel movement, sleep evaluation, and vomiting questionnaires. Treatment comparisons for the change in response from baseline were assessed.

The safety analysis set included all randomized subjects who received at least 1 dose of study drug.

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

SYNOPSIS (CONTINUED)

SUMMARY - CONCLUSIONS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

Demographic and baseline characteristics were balanced across the treatment groups. Most subjects were white (91%). Across the treatment groups, 51% of subjects were male and 61% were <65 years of age. The majority of subjects were enrolled in the US or Canada (53% and 34%, respectively). In total, 69% of subjects were categorized as having severe baseline pain intensity.

EFFICACY RESULTS:

Primary efficacy variable: Both tapentadol IR treatment groups showed a significant (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain for the primary efficacy variable of 5-day SPID compared with placebo with LOCF imputation. Both tapentadol IR groups showed similar efficacy (mean 5-day SPID: 229.2 and 223.8 in the tapentadol IR 50 mg and 75 mg groups, respectively). Oxycodone HCl IR 10 mg (mean 5-day SPID: 236.5) also showed a significant (nominal p-value <0.001) difference from placebo (mean 5-day SPID: 130.6), validating the study assay sensitivity. In addition, analyses of mean 5-day SPID results based on BOCF imputation also indicated significant improvement in pain of both tapentadol IR groups compared with placebo (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure). Analyses of mean 5-day SPID results based on all other imputation strategies (WOCF and modified LOCF) and based on the per protocol analysis set confirmed these results (all nominal p-values <0.001).

Secondary efficacy variables: The results for secondary efficacy variables supported the primary variable results. For secondary pain scale variables that were statistically tested (SPID, TOTPAR, and SPRID), both tapentadol IR treatment groups showed significant improvements (all nominal p values <0.001) compared with the placebo group at all time points (2 days, 5 days, and 10 days). For variables not statistically tested (PID, PAR, and PRID), numerical indications of efficacy were observed.

For PGIC, 49% of subjects in the tapentadol IR 50 mg group, 42% of subjects in the tapentadol IR 75 mg group, and 41% of subjects in the oxycodone HCl IR 10 mg group reported “very much improved” or “much improved” in the overall impression of change compared with 21% of subjects in the placebo group. All active treatment groups showed significant improvements compared with placebo (nominal p-values for both tapentadol IR groups <0.001; nominal p-value for oxycodone HCl IR = 0.005).

For time to first rescue medication use, the percentage of subjects who took rescue medication was low and similar across treatment groups (4% in the placebo, 3% in the tapentadol IR 50 mg, 3% in the tapentadol IR 75 mg, and 1% in the oxycodone HCl IR groups). As a result, there were no significant differences in the distribution of time to first rescue medication between any active treatment group and placebo. More subjects taking tapentadol IR demonstrated a minimum reduction in pain intensity of 30% or 50% compared with subjects taking placebo (e.g., 28% of subjects in the tapentadol IR 50 mg group had a 50% reduction in pain intensity at Day 5 compared with 13.0% of subjects in the placebo group [p-value 0.003]). A significant difference from placebo was found only for tapentadol IR 50 mg in the distribution of responder rates (nominal p-value = 0.011, Gehan test). A post-hoc analysis using the logrank test revealed that there were significant differences between each of the tapentadol IR groups and placebo (nominal p-value <0.001 for tapentadol IR 50 mg and 0.003 for tapentadol IR 75 mg).

Compared with oxycodone HCl IR 10 mg, both tapentadol doses (50 mg and 75 mg) were non-inferior to oxycodone HCl IR 10 mg based on 5-day SPID with the lower bound of the 95% confidence interval being within the prespecified non-inferiority margin.

SYNOPSIS (CONTINUED)

SAFETY RESULTS:

The overall percentage of subjects with treatment emergent adverse events (TEAEs) during the treatment period for tapentadol IR groups increased with increasing dose. The percentage for all active-treatment groups was higher than in the placebo group.

The most common TEAEs were dizziness, somnolence, nausea, vomiting, constipation, fatigue, and pruritus. Comparing subjects with the higher tapentadol IR dose (75 mg) with those receiving oxycodone HCl IR 10 mg, the incidence was lower for nausea (21% and 41%, respectively), vomiting (14% and 34%, respectively), constipation (7% and 26%, respectively), and pruritus (5% and 15%, respectively) and comparable for dizziness (26% and 23%, respectively), somnolence (10% and 12%, respectively), and fatigue (7% and 10%, respectively).

There were no deaths during the study, and there were no serious TEAEs for subjects in the tapentadol IR groups. The highest incidence of TEAEs leading to discontinuation was observed in subjects in the oxycodone HCl IR group (29%) compared with subjects in the tapentadol IR groups (13% for tapentadol IR 50 mg and 18% for tapentadol IR 75 mg) and in the placebo group (4%). The most frequent adverse events leading to treatment discontinuation were dizziness, somnolence, nausea, vomiting, and constipation.

Most adverse events were of mild to moderate intensity. Among the most common TEAEs, a higher percentage of severe cases was reported for subjects in the oxycodone HCl IR group than for subjects in the tapentadol IR groups (either dose). The most common TEAEs were mainly considered related to study medication. Apart from the majority of events which did not need countermeasures, medication was frequently employed for GI events, especially for oxycodone. Evaluation of subgroups revealed higher incidences of TEAEs in female subjects.

Statistical testing was performed for nausea, vomiting, and constipation. Significant (p-value <0.05) increases in the incidence of these TEAEs were observed for all active treatment groups compared to placebo, except for vomiting and constipation in which no significant difference from placebo was observed for the tapentadol IR 50 mg group. The odds ratios for vomiting, nausea, and constipation rates relative to placebo increased with increasing doses of tapentadol IR. The odds ratios for oxycodone HCl IR 10 mg were higher than those for the higher dosing regimen of tapentadol IR tested (tapentadol IR 75 mg) for all 3 adverse events. In addition, for the composite of nausea and vomiting and for constipation tapentadol IR 50 mg and 75 mg both demonstrated lower incidences (nominal p-value <0.001) compared with oxycodone HCl IR 10 mg.

For the treatment period, examination of mean values over time did not reveal clear or consistent patterns for laboratory evaluations, urinalysis, vital signs, or ECG. Examination of individual abnormal values for laboratory, vital signs, and ECG revealed mainly single occurrences of outlying values and sporadic TEAEs. The incidence of these single occurrences of variations was low and did not reveal a clear pattern. There was no apparent association of mean changes with tapentadol IR administration.

Separate evaluations of vomiting and multiple components of the bowel movement questionnaire supported the conclusion that a higher number of subjects in all active treatment groups experienced constipation and vomiting compared with subjects in the placebo group. Furthermore, the incidence of these events was lower with tapentadol IR groups compared with the oxycodone HCl IR 10 mg group. For the sleep evaluations, the results indicated that the overall quality and duration of sleep was better in subjects who used active treatments.

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:

T Tapentadol IR, in a fixed-dose regimen (50 mg or 75 mg) administered every 4 to 6 hours, was effective in an outpatient setting over 10 days, providing pain relief to subjects with moderate to severe pain from end-stage joint disease of the knee or hip. Both doses of tapentadol IR were well tolerated, with a safety profile similar to that of other centrally acting analgesics with μ-opioid activity. Prospectively defined adverse event comparisons with oxycodone HCl IR indicated improved GI tolerability with tapentadol IR 50 mg and 75 mg (specifically nausea, vomiting, and constipation). CNS tolerability (specifically somnolence and dizziness) was similar.

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