SYNOPSIS

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Name of Sponsor/Company	Grünenthal GmbH; in codevelopment with Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	To be determined
Name of Active Ingredient	Tapentadol HCl

Protocol No.: R331333-PAI-3008 (KF5503/11)

Title of Study: A Randomized Double-Blind, Placebo- and Active-Control, Parallel-Arm, Phase 3 Study With Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of Tapentadol Extended-Release (ER) in Subjects With Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee

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Publication (Reference): None

Study Period: 07 February 2007 to 15 July 2008

Phase of Development: Phase 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of orally administered tapentadol ER at doses 100 to 250 mg twice daily (b.i.d.) in subjects with moderate to severe chronic pain from osteoarthritis (OA) of the knee. Secondary objectives included the collection of pharmacokinetic information for dose verification and population pharmacokinetic analyses.

Methods: This was a randomized, multicenter, double-blind, parallel group study, comparing the efficacy and safety of controlled dose-adjustment regimens of tapentadol ER (100 to 250 mg b.i.d.), oxycodone controlled release (CR, 20 to 50 mg b.i.d.), and placebo in subjects with moderate to severe chronic pain from OA of the knee. The study consisted of 5 periods: screening (duration up to 14 days, Visit V1), washout (duration 3 to 7 days, Visit V2), double-blind treatment period with titration (duration 3 weeks, Visits T1, T2, and T3) and maintenance (duration 12 weeks, Visits M1 to M8). A follow-up visit and a follow-up telephone call (adverse events recording only) occurred within 4 days and 10 to 14 days after last study drug intake, respectively. During titration, the starting doses were tapentadol ER 50 mg, oxycodone CR 10 mg, or placebo b.i.d. for 3 days. The dose was then increased to tapentadol ER 100 mg b.i.d., oxycodone CR 20 mg b.i.d., or placebo b.i.d. and subjects were to receive this dose for the next 4 days. Thereafter, increases in the dose were allowed in increments of tapentadol ER 50 mg b.i.d., oxycodone CR 10 mg b.i.d., or placebo to achieve a stable optimal dose. During the titration period paracetamol/acetaminophen was allowed as required as additional analgesic medication (rescue medication), limited to a total of 1000 mg daily. Before entering the maintenance period, subjects had to demonstrate that they had been stabilized at the optimal dose for the last 3 days of the titration period without any rescue medication. During the maintenance period, subjects continued the study drug intake for 12 weeks. During the titration and maintenance periods dose increases in increments of tapentadol ER 50 mg b.i.d., oxycodone CR 10 mg b.i.d., or placebo b.i.d. were allowed every 3 days, and decreases in the dose using the same decrements were allowed at any time. The maximum (minimum) tapentadol ER and oxycodone CR doses allowed were 250 mg (100 mg) and 50 mg (20 mg) b.i.d., respectively. Subjects who completed the study were offered the opportunity to continue in an open-label extension (OLE, PAI-3010/KF18) study.

Number of Subjects (planned and analyzed): Planned: 942 subjects (314 per treatment group); randomized: 1030 subjects; analyzed for safety (Safety Analysis Set): 1023 subjects; analyzed for efficacy - full analysis set (ITT): 1023 subjects; and per protocol analysis set (PP): 903 subjects; analyzed for tapentadol serum concentrations: 1153 samples from 336 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were men and non-pregnant, non-lactating women, at least 40 years old, diagnosed with of OA of the knee based on American College of Rheumatology (ACR) criteria and functional capacity class of I to III present for at least 3 months, had baseline score of ≥5 on an 11-point NRS (moderate to severe pain), calculated as the average pain intensity during the last 72 hours prior to randomization, were taking analgesic medications for the condition for at least 3 months prior to screening and were dissatisfied with current therapy; if they required opioid treatment, they took daily doses of opioid-based analgesic equivalent to ≤160 mg of oral morphine.

Test Product, Dose and Mode of Administration, Batch No.: Tapentadol ER film-coated oral tablets in doses of 50 mg (Lot PD2275, PD2278, PD2347, PD2395, PD2555, PD2567), 100 mg (Lot PD2281, PD2434), 150 mg (Lot PD2284, PD2359), 200 mg (PD2287, PD2455).

Reference Therapy, Dose and Mode of Administration, Batch No.: Oxycodone CR (OxyContin®) overencapsulated oral tablets in doses of 10 mg (Lot PD2245, PD2321), 20 mg (Lot PD2246, PD2322), 30 mg (Lot PD2247, PD2417), 40 mg (Lot PD2248, PD2324).

The placebo formulations supplied for this study were identical in appearance to tapentadol ER and oxycodone CR containing study drugs. Tapentadol ER placebo had Lot PD2290, PD2293, PD2296, PD2299, PD2304, and oxycodone CR placebo had Lot PD2249, PD2320, PD2325, PD2326.

Duration of Treatment: The study drugs were administered b.i.d. over 15 weeks including the titration period (3 weeks) and controlled-dose adjustment maintenance period (12 weeks) for each individual study participant.

Criteria for Evaluation: Efficacy: The efficacy evaluations consisted of pain intensity assessment (11-point NRS, average pain, b.i.d.), Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC) scores; sleep questionnaire scores; Patient global impression of change (PGIC); time to withdrawal due to lack of efficacy (subject perception that the study drug did not sufficiently reduce pain); EuroQol-5 Dimension Health Questionnaire (EQ-5D) and Short Form 36® Health Survey (SF-36) assessments.

Safety: The safety evaluations consisted of adverse events, Patient Assessment of Constipation (PAC-SYM) scores, physical examination, vital signs (pulse rate, respiratory rate, blood pressure [supine or sitting]), clinical laboratory values, 12-lead ECG, Clinical Opioid Withdrawal Scale (COWS), and Subjective Opioid Withdrawal Scale (SOWS).

Pharmacokinetics: Blood samples were collected at visits specified in the protocol and the serum concentrations of tapentadol are presented in this report. These blood samples were also collected to obtain population PK data. The population PK analyses will be reported separately.

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

Pharmacogenomics: One blood sample per subject was collected at screening from subjects who signed an informed consent for pharmacogenomic testing. No pharmacogenomic analyses were performed. Any analyses performed at a later date will be reported separately.

Statistical Methods:

Efficacy: The primary analysis was performed on the full analysis set, intent-to-treat (ITT), which consisted of all randomized subjects who received at least 1 dose of the study drug, and is equal to the safety analysis set. The per protocol set consisted of all randomized subjects who were in the full analysis set, and who received study drugs regularly and were compliant with the protocol as defined in the Statistical Analysis Plan.

Primary Efficacy Analysis: For the US regulatory authority, the primary efficacy endpoint was defined as the change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point NRS. For non-US regulatory authorities, the primary efficacy endpoint was defined as the change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point NRS. The primary endpoint for 1 region was considered as a secondary endpoint in the other. The primary null hypothesis to be tested for the study was that the tapentadol ER group was not different from placebo group in the primary endpoint. The alternative hypothesis was that the tapentadol ER group was different from placebo group in the primary endpoint. The primary efficacy analyses on the primary endpoint was an analysis of covariance (ANCOVA) model with treatment and pooled analysis center as factors and baseline pain intensity score as a covariate. Treatment effect of tapentadol ER versus placebo was estimated based on least-square means of the difference (LSD). The p-value for the treatment difference along with the 2-sided 95% CI were presented. The test for the primary efficacy analysis was 2-sided at 0.05 alpha level. The primary imputation method was the last observation carried forward (LOCF). Sensitivity analyses were performed with various imputation methods (baseline observation carried forward [BOCF], worst observation carried forward [WOCF], placebo mean imputation [PMI], and modified BOCF) to evaluate the robustness of the observed treatment effects on the primary efficacy endpoint.

Secondary Efficacy Analyses: The responder rate was defined as the proportion of subjects achieving various levels of pain improvement based on the percent change from baseline at Week 12 of the maintenance period on an 11-point NRS. The distribution of responder rates in increments of 10% from 10% to 100% was presented graphically for each treatment group. The distribution of responder rates at Week 12 was estimated by the Kaplan-Meier estimate and compared among the treatment groups using log-rank test. In addition, responder rates for achieving at least 30% and 50% improvement in $CBPIA_{m12}$ were compared using the CMH test, presenting the p-value for the pairwise differences in responder rates between the treatment arms. The PGIC assessments were summarized with number and percentage of subjects by treatment group as per visit windows and analyzed at the end of the maintenance period using the CMH test. The change from baseline of the 3 subscale scores as well as global WOMAC score at each time point (based on the visit windows) was summarized using descriptive statistics and analyzed using a repeated measures model. The model was fitted using PROC MIXED fitting time point as the repeated factor and with treatment and pooled analysis center as factors and baseline value as a covariate. For the sleep questionnaire, descriptive statistics for the absolute values and changes from baseline of Items 1 and 3 of the sleep questionnaire were provided by week and endpoint. A frequency distribution of responses to sleep quality (Items 2 and 4) was presented at each visit by treatment group. Item 4 was also analyzed using the CMH test at each visit. A weighted EQ-5D health status index was derived and summarized descriptively for each of the treatment groups. Also, an ANCOVA model with treatment and pooled analysis center as factors and baseline value as covariate was built for the change from baseline to endpoint data on the weighted EQ-5D index. Change from baseline on EQ-5D to endpoint was summarized descriptively. For the SF-36 Health Survey, the change from baseline to endpoint was summarized descriptively for each of the 8 dimensions using the transformed scale. An ANCOVA model was applied to these SF-36 data with treatment and pooled analysis center as factors and baseline value as covariate.

Exploratory Efficacy Analysis: Descriptive statistics were provided for the primary efficacy endpoint by subgroups (sex, racial/ethnic group, age group, baseline pain intensity, prior opioid use, country, pooled analysis center, dose category, dose range, number of dose changes), as well as average pain intensity scores during the double-blind treatment period and for subjects who had diary data recorded after the end of treatment. The primary efficacy endpoint was performed on the per protocol analysis set as an exploratory analysis.

Pharmacokinetics: Descriptive statistics were performed on actual and dose normalized serum concentrations of tapentadol.

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. Treatment comparisons for the change in response from baseline were assessed. Opiate withdrawal effects were assessed using descriptive statistics of the COWS and SOWS scores. Treatment comparisons for COWS and SOWS scores were performed using the CMH test and analysis of variance (ANOVA)

model. Constipation was evaluated using PAC-SYM subscales and overall scores by subgroups (with and without TEAEs of constipation)

Pharmacogenomics: No pharmacogenomic analyses were performed.

RESULTS:

SUBJECT DISPOSITION AND STUDY COMPLETION/WITHDRAWAL INFORMATION: The percentage of subjects completing the study was greater in the placebo (60.2%) and tapentadol ER (52.6%) groups than in the oxycodone CR group (34.5%). The most common reasons for study discontinuation in the active-treatment groups were adverse events followed by subject choice (subject withdrew consent). Across all treatment groups, discontinuations were higher during the titration period than during the maintenance period. The percentage of subjects who discontinued treatment due to adverse events was greater in the oxycodone CR group (43.0%) than in the tapentadol ER (19.2%) or placebo (6.5%) groups.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: Demographic and baseline characteristics were comparable across the treatment groups. The majority of subjects were female (60.4%), white (75.5%), and younger than 65 years of age (74.1%). In addition, most subjects had not taken opioids during the 3 months prior to the screening visit (67.6%) and were categorized as having severe baseline pain intensity (NRS $\geq$ 6, 83.4%).

EXPOSURE: During the 15-week double blind treatment period, subjects in the placebo and tapentadol ER groups remained on study drug longer than subjects in the oxycodone CR group (median treatment duration: 105, 104, and 26 days, respectively). During the titration period, the median of the modal total daily dose was 300 mg in the tapentadol ER group and 40 mg in the oxycodone CR group. During the 12-week maintenance period, the median of the modal total daily dose was 400 mg for tapentadol ER and 80 mg for oxycodone CR.

PHARMACOKINETICS: Within the intended dose range of 100 to 250 mg, mean tapentadol serum concentrations generally increased with increasing dose.

EFFICACY RESULTS: For the change from baseline in the average pain intensity at Week 12 of the maintenance period for US regulatory authority and the change from baseline in the average pain intensity over the 12 week maintenance period for non-US regulatory authorities (primary efficacy variables), tapentadol ER showed a statistically significant reduction in average pain intensity compared to placebo at both Week 12 of the maintenance period and the overall maintenance period using LOCF (both p-values <0.001). The comparison between oxycodone CR and placebo demonstrated a statistically significant reduction in average pain intensity for the overall maintenance period ($p = 0.049$) and a numeric reduction in average pain intensity at Week 12 that was not statistically significant ($p = 0.069$).

Sensitivity analyses were performed on the primary efficacy endpoint using imputation methods BOCF, WOCF, PMI, and modified BOCF. Statistically significant reductions in the average pain intensity for tapentadol compared to placebo were identified when the modified BOCF was applied at Week 12 of the maintenance period ($p =0.009$) and the overall maintenance period ($p =0.01$), and when the PMI method was applied to both endpoints ($p=0.001$). There were no statistically significant differences between tapentadol ER and placebo when the more conservative BOCF and WOCF methods were applied. For the comparison between oxycodone CR and placebo groups, there was a statistically significant greater reduction in the average pain intensity in the placebo group than in the oxycodone CR group when BOCF, WOCF, and the modified BOCF methods were applied to each endpoint. The oxycodone CR group demonstrated a greater reduction in average pain intensity compared to placebo in the PMI method only, although the difference was not statistically significant. The oxycodone CR results were influenced by the high discontinuation rate of subjects in this group. An analysis using observed cases for subjects who completed treatment confirmed the results of the primary analysis using LOCF.

Subjects with severe baseline pain tended to have greater numerical improvements in pain intensity scores than subjects with moderate baseline pain for the overall maintenance period. For subjects in the tapentadol ER group with baseline pain intensity scores categorized as severe, statistically significant reductions in average pain intensity scores compared to placebo were reported for Week 12 of the maintenance period and the entire maintenance period ($p=0.002$ and $p<0.001$, respectively). Differences in pain intensity for subjects with moderate baseline pain (which had a lower sample size) were not statistically significant. For the oxycodone group, the difference in pain intensity scores from placebo was not statistically significant in either the severe or moderate categories. The mean changes in average pain scores from baseline to Week 12 of the maintenance period and the overall maintenance period showed a greater difference between tapentadol and placebo for subjects who took prior opioid medications than for subjects who did not take prior opioids. Similar results were observed for the comparison between the oxycodone CR and placebo group.

There was no significant difference between tapentadol ER and placebo groups in the distribution of percent improvement from baseline in average pain intensity (based on NRS) at the last week of the maintenance period. A statistically significantly higher percentage of subjects in the placebo group showed a greater improvement than in the oxycodone group ($p=0.002$). The proportion of tapentadol ER subjects showing at least 50% improvement in pain intensity at Week 12 of the maintenance period was significantly greater than placebo ($p=0.027$). Statistical significance for tapentadol ER compared to placebo, was not demonstrated for subjects showing at least 30% improvement in pain intensity. Oxycodone CR was significantly inferior to placebo in both the 50% and 30% improvement in pain intensity rates.

The distribution of time to treatment discontinuation due to lack of efficacy showed that a statistically significantly higher percentage of subjects in the placebo group discontinued treatment for this reason compared to the tapentadol ER and oxycodone CR groups ($p<0.001$ for both treatment groups). Significant advantages over placebo in PGIC scores was seen in subjects from both the tapentadol ER (59% reported “much improved” or “very much improved”) and oxycodone CR (47% reported “much improved” or “very much improved”) groups ($p<0.001$ and $p=0.018$, respectively) at the end of the double-blind treatment period. The difference in the WOMAC global score at Week 12 of the maintenance period was greater for tapentadol ER and oxycodone CR relative to placebo and these differences were statistically significant ($p=0.005$ and $p=0.038$, respectively).

For the SQ scores, improvement from baseline in the quality of sleep (Item 4) was observed in all treatment groups at endpoint, and neither tapentadol ER nor oxycodone CR were significantly different from placebo. Tapentadol ER was more effective than oxycodone CR and placebo in improving EQ-5D health status index at endpoint ($p<0.001$ and $p=0.004$, respectively). Significant improvement in the physical component summary of the SF-36 health survey was seen in subjects receiving tapentadol ER compared to placebo. Subjects in the placebo group showed significant improvement over the oxycodone CR group on the mental component summary.

SAFETY RESULTS: The overall incidence of TEAEs was higher in the oxycodone CR group (87.4%) than the tapentadol ER (75.9%) or placebo (61.1%) groups. The most common adverse events in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The incidence of nausea, constipation, vomiting, and somnolence was substantially lower in the tapentadol ER group (21.5%, 18.9%, 5.2%, 10.8%, respectively) than the oxycodone CR group (36.5%, 36.8%, 17.8%, 19.6%, respectively).

One subject in the oxycodone CR group died during the study. More subjects in the oxycodone CR group (2.9%) reported serious adverse events compared to the tapentadol ER (1.2%) and placebo (1.8%) groups. More subjects in the oxycodone CR group (42.7%) had TEAEs that led to study discontinuation than the tapentadol ER (19.2%) or placebo (6.5%) groups. The majority of TEAEs that led to study discontinuation in the oxycodone CR group were from the gastrointestinal disorders SOC and nervous system disorders SOC.

Most adverse events were of mild to moderate intensity. A greater percentage of subjects in the oxycodone CR group experienced TEAEs of nausea, constipation, and vomiting that were moderate or severe in intensity compared to the tapentadol ER group. In both active treatment groups, nausea and vomiting were reported more often for female than male subjects.

No clinically important treatment-related changes in laboratory values, vital signs or ECG findings were observed.

PAC-SYM assessments indicated a significant advantage for tapentadol ER over oxycodone CR for the overall score and the overall abdominal, rectal, and stool subscale scores. In all 3 treament groups, most subjects reported no withdrawal symptoms following discontinuation of treatment. The COWS score indicated a generally low degree of opioid withdrawal symptoms following abrupt discontinuation of treatment with all assessed subjects having no or mild or moderate withdrawal. There were no significant differences between the active-treatment groups compared with the placebo group in the SOWS assessment, regardless of opioid use at the time of the SOWS assessment.

CONCLUSION: Tapentadol ER was effective when administered 100 to 250 mg b.i.d. in a controlled dose-adjustment design for up to 15 weeks in subjects with moderate to severe chronic pain due to OA. The efficacy results were more robust than for oxycodone CR as demonstrated by the results with the more conservative imputation methods and, reflective of the improved tolerability and reduced rate of discontinuation of subjects in the tapentadol ER group. The safety profile of tapentadol ER is consistent with the profile expected for a centrally acting analgesic with mu-opioid receptor agonist activity but with reduced incidence of constipation, nausea, vomiting, somnolence, and pruritus, compared with oxycodone CR. The improved overall tolerability of tapentadol ER compared to oxycodone CR is clinically important as it allows subjects to remain on treatment for a longer period of time. These results demonstrate that tapentadol ER has analgesic efficacy with a favorable tolerability profile in subjects with moderate to severe chronic pain due to OA.

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