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-3011 (KF5503/23), CR013399

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 Low Back Pain.

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Publication (Reference): None

Study Period: 21 February 2007 to 01 May 2008

Phase of Development: Phase 3

Objectives: The primary objective of the 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 low back pain (LBP). 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 tapentadol ER (100 to 250 mg b.i.d.), oxycodone controlled release (CR) (20 to 50 mg b.i.d.), and placebo b.i.d. in subjects with moderate to severe chronic LBP. The study consisted of a screening period (duration up to 14 days), a washout period (duration 3 to 7 days), a double-blind active treatment period with titration (duration 3 weeks) and maintenance (duration 12 weeks). During titration, the starting dose was tapentadol ER 50 mg b.i.d., oxycodone CR 10 mg b.i.d., or placebo b.i.d for 3 days (6 consecutive doses). 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 (i.e., the dose that provided meaningful improvement in pain with acceptable side effects in the subject's perception). 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 into the maintenance period, subjects had to maintain a stable optimal dose for the last 3 days of the titration period without any rescue medication. During the maintenance phase, subjects were to continue their study drug intake for 12 weeks. 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 increments 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. 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. Subjects who completed the study were offered the opportunity to continue in an open-label extension (OLE) study (PAI-3010/KF18).

Number of Subjects (planned and analyzed): Planned: 942 subjects (314 per treatment group); randomized: 981 subjects; analyzed for efficacy (intent-to-treat analysis set [ITT]): 958 subjects, (per-protocol [PP] analysis set): 745 subjects; analyzed for safety: (safety analysis set): 965 subjects; 695 samples from 289 subjects were included in the descriptive statistical analysis of tapentadol serum concentrations.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were men and non-pregnant, non-lactating women, at least 18 years old, had diagnosis of LBP of non-malignant origin present for at least 3 months, were taking analgesic medications for the condition for at least 3 months prior to screening and were dissatisfied with current therapy, and had baseline score of ≥5 on an 11-point numerical rating scale (NRS) calculated as the average pain intensity during the last 72 hours prior to randomization; 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 Nos. PD2275, PD2278, PD2347, PD2395, PD2555, PD2567, and PD2278), 100 mg (Lot Nos. PD2281 and PD2434), 150 mg (Lot Nos. PD2284 and PD2359), and 200 mg (Lot Nos. PD2287, PD2287, and PD2455).

Reference Therapy, Dose and Mode of Administration, Batch No.: Oxycodone CR: Overencapsulated OxyContin® oral tablets in doses of 10 mg (Lot Nos. PD2321 and PD2245), 20 mg (Lot Nos. PD2246 and PD2322), 30 mg (Lot Nos. PD2247, PD2323, and PD2417), and 40 mg (Lot Nos. PD2248 and PD2324).

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

Duration of Treatment: Study drug was administered b.i.d.; active treatment (15 weeks) included the titration phase (3 weeks) and controlled-dose adjustment maintenance phase (12 weeks) for each individual study participant. At the end of treatment, study drug was stopped without tapering.

Criteria for Evaluation: Efficacy**:** The efficacy evaluations consisted of pain intensity assessments (b.i.d. based on 11-point NRS, average pain), Patient Global Impression of Change (PGIC), Brief Pain Inventory (BPI), Sleep Questionnaire (SQ), time to discontinuation due to lack of efficacy (subject perception that the study drug did not sufficiently reduce pain), EuroQol-5 Dimension (EQ-5D) scores, 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.

Pharmacogenomics: One blood sample per subject was collected at screening from subjects who signed an informed consent for pharmacogenomic testing.

Statistical Methods:

Efficacy: The ITT analysis set was used for the efficacy analyses and included all randomized subjects who received at least 1 dose of study drug. Subjects from Sites 001487 and 001432, and Subject 115708 from Site 001473 were excluded from the ITT analysis set because of major audit findings.

Primary Efficacy Analysis: Two different primary endpoints were used to region-specific regulatory requirements. For the United States of America (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 analysis on the primary endpoint was an analysis of covariance (ANCOVA) with treatment and pooled analysis centers 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% confidence interval (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. Analysis of primary endpoints using per-protocol set and safety analysis set was also performed.

Secondary Efficacy Analyses: The secondary efficacy analyses were performed using the LOCF imputation method for the ITT analysis set to compare tapentadol ER with placebo. As exploratory analysis, the assay sensitivity (oxycodone CR versus placebo) comparison and differentiation between tapentadol ER and oxycodone CR was performed using the same model described for the primary efficacy.

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 (responder rate). 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 the log rank test. Responder rates for achieving at least 30% and 50% improvement in the change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 were compared using the Cochran-Mantel-Haenszel (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 and analyzed at the end of the maintenance period using the CMH test. Descriptive statistics were provided for each of the BPI pain interference score, pain subscale, and the total score at each visit, and for the corresponding changes from baseline. Each of the pain interference score, pain subscale, and total score were analyzed using separate ANCOVA models, with treatment and pooled analysis center as factors and baseline value as covariate. The LS mean treatments and differences and the p-value for the treatment difference with the 95% CI were presented. Descriptive statistics for the absolute values and changes from baseline of Items 1 to 3 of the SQ were provided by week and endpoint. A frequency distribution of responses to sleep quality (Item 4) was presented at each visit by treatment group. Item 4 was also analyzed using the CMH test at the end of the double-blind treatment period. Changes in response, from baseline to each visit and at endpoint, for item 4 were also presented in a shift table. A sensitivity analysis was performed excluding all questionnaires with more than 1 record per day. The distribution of the time to treatment discontinuation due to lack of efficacy was estimated by the Kaplan Meier estimate and compared among the treatment groups using the log rank test. A weighted EQ-5D health status index was derived and summarized descriptively, including changes from baseline, 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. The LS mean treatments and differences and the p-value for the treatment difference with the 95% CI were presented. Two summary SF-36 scale scores were computed based on weighted combinations of the 8 subscale scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS). For each of the 8 dimensions, using the transformed scale, and for the PCS and MCS summary scores, the change from baseline to endpoint was summarized descriptively and ANCOVA models for treatment comparisons were built using treatment and pooled analysis center as factors and baseline value as covariate. The LS means for each treatment group, LS mean differences, and the corresponding p-values and 95% CI for the treatment difference were presented.

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.

Pharmacokinetics: Serum concentrations as a function of time were explored for tapentadol.

Safety: The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Two subjects were randomized and treated twice; therefore, data from the second randomization were excluded from the safety analysis set. Descriptive statistics and frequency analysis (percentage of subjects) by treatment group were used to assess safety. Incidence of the treatment-emergent adverse events (TEAEs) in the gastrointestinal (GI) system, including nausea, vomiting, and constipation, were summarized and compared among treatment groups using the CMH test. Time to the onset of the first treatment-emergent nausea, vomiting, and constipation and time to discontinuation due to TEAE were also presented in Kaplan-Meier plot and compared using log-rank test. Odds ratios of the event incidence were calculated for tapentadol ER versus oxycodone CR. 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 study treatment was greater in the tapentadol ER group (54.1%) and placebo group (50.5%), than in the oxycodone CR group (43.3%). The most common reasons for treatment discontinuation was adverse events in the active-treatment groups and lack of efficacy in the placebo group. The percentage of subjects who discontinued treatment due adverse events in the tapentadol ER group (16.7%) was approximately half that report in the oxycodone CR group (32.3%); most of these events were reported during the titration period.

The median time to treatment discontinuation in the double-blind treatment period was similar in the tapentadol ER (118 days) and placebo groups (119 days) and significantly longer in the tapentadol ER group than in the oxycodone CR group (118 days vs. 62 days; $p < 0.001$).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: Approximately 58% of all subjects in the safety analysis set were female. Most subjects were white (73.3%) and less than 65 years old (84.6%). Mean baseline pain intensity score, based on the 11-point NRS was 7.5, with 88.5% of subjects categorized as having severe pain (baseline score at least 6). Opioid analgesics were taken by 53.4% of subjects during the 3-month period prior to the screening visit. Demographic and baseline characteristics were similar among the treatment groups.

EXPOSURE: The median treatment duration (i.e., the duration on study drug not counting zero dose days) during the entire 15-week double-blind treatment period was longer in the placebo (102 days) and tapentadol ER (103 days) groups compared with the oxycodone CR group (62 days). Overall, the average of the mean total daily dose (TDD) during double-blind treatment was 313.2 mg in the tapentadol ER group and 53.0 mg in the oxycodone CR group. During the 12-week maintenance period, the mean TDD was 381.8 mg in the tapentadol ER group and 71.4 mg in the oxycodone CR group.

Subjects in all 3 groups received the modal dose (the most frequently used dose) for at least 93% of the time during the 12-week maintenance period with only a small increase (<5%) in the mean TDD, indicating that most subjects were maintained on a stable dose. The median duration of treatment during the maintenance period was comparable among the 3 groups (12 weeks). More subjects in the tapentadol ER and placebo groups than in the oxycodone CR group received a high dose (i.e., average TDD of≤400 mg for tapentadol ER and ≤80 mg for oxycodone CR). Subjects remained at a high dose for a longer period of time in the tapentadol ER (median = 40 consecutive days) and placebo (57.0 consecutive days), and than in the oxycodone CR group (23 consecutive days).

DRUG SERUM CONCENTRATION MEASUREMENTS: Within the intended dose range of 100 mg to 250 mg b.i.d., mean tapentadol serum concentrations generally increased with increasing dose.

EFFICACY RESULTS: On the primary efficacy variable, the tapentadol ER group was statistically superior to the placebo group at both Week 12 of the maintenance period and over the entire 12-week maintenance period using LOCF (p-values <0.001); a difference of -0. 8 at Week 12 of the maintenance period and a difference of -0.7 for overall maintenance period between the tapentadol ER group and placebo. The comparison between oxycodone CR and placebo also demonstrated statistically significant differences (p-values <0.001) in favor of oxycodone CR at these time points confirming assay sensitivity (a difference of -0. 9 at Week 12 of the maintenance period and a difference of -0.8 for overall maintenance period).

Results of the primary endpoint using more conservative imputation methods were consistent with the primary analysis with significant improvement of pain for the tapentadol ER group compared with the placebo group for all imputation methods (BOCF, WOCF, modified BOCF, and PMI). For the comparison between oxycodone CR and placebo, there were statistically significant differences compared with placebo in all imputations except at Week 12 of the maintenance period when the BOCF and WOCF imputation methods were applied. This is likely to be a reflection of the higher discontinuation rate in the oxycodone CR group compared with tapentadol ER group.

The results for the PP and safety populations using LOCF were consistent with those observed for the ITT population based on the same ANCOVA models.

There were statistically significant reductions in average pain intensity in the tapentadol ER group compared with placebo at both Week 12 of the maintenance period and the overall maintenance period for subjects with moderate baseline pain (p-values ≤0.027) and subjects with severe baseline pain scores (p values <0.001). Subjects with moderate baseline pain tended to have greater improvements in pain intensity scores than subjects with severe baseline pain.

Tapentadol ER showed statistically significant reductions in average pain intensity scores compared with placebo at Week 12 of the maintenance period and over the entire maintenance period for subjects with prior opioid use (p-values ≤0.015) and for subjects with no prior opioid use (p-values ≤0.001). Similar results were observed in the oxycodone CR group. In the tapentadol ER group, subjects with no prior opioid use tended to have greater improvements in pain intensity scores than subjects with prior opioid use. Similar results were not observed for the oxycodone CR group. In the oxycodone CR group, subjects with prior opioid use had greater improvements from baseline in pain scores than subjects with no prior opioid use.

Subjects enrolled at sites in the US tended to have greater improvements in pain intensity scores than subjects enrolled at sites in Canada; however, more subjects were enrolled at US sites (n=262 to 273) than Canadian sites (n=48 to 53). There were no differences between treatment groups for the subgroups of race in the primary efficacy variable. In the placebo and tapentadol ER groups, greater improvements in average pain intensity scores were observed for females than males and for subjects less than 65 years old than for subjects 65 years of age or older.

There was a statistically significantly greater proportion of responders at Week 12 of the maintenance period in the tapentadol ER group than in the placebo group (p=0.004); the difference between the oxycodone CR and placebo groups was not significant (p=0.090). The difference in the proportion of subjects showing at least 30% improvement (p<0.001) and at least 50% improvement (p=0.016) was statistically significant when comparing tapentadol ER to placebo; no statistically significant difference was noted for the comparison of oxycodone CR and the placebo group.

For the distribution of PGIC scores at endpoint, there was a statistically significant difference in the tapentadol ER group (56% improved, includes ‘much’ and ‘very much’ improved categories) compared with the placebo group (33% improved; p<0.001). Similar results were noted for the oxycodone CR group (60% improved) compared with the placebo group (p <0.001).

The Brief Pain Inventory scores at Week 12 of the maintenance period showed greater improvement from baseline in Item 1 (pain other than everyday kinds of pain) and Item 8 (percent pain relief) in the 2 active-treatment groups compared with the placebo group. At endpoint, both active-treatment groups

showed statistically significant reductions in pain interference score (Items 9A to 9G), pain subscale scores (Items 3 to 6), and the total score (Items 9A to 9G, Items 3 to 6) compared with placebo (p-values ≤0.002 for all comparisons except pain interference score for oxycodone CR with p=0.023).

For the SQ scores, there was a statistically significant improvement from baseline in the quality of sleep (Item 4) in the tapentadol ER group compared with the placebo group (p=0.003) at endpoint. Results for the comparison of oxycodone CR and placebo were not significant.

There was a statistically significant difference in the distribution of time to treatment discontinuation due to lack of efficacy relative to placebo (log-rank p <0.001) for tapentadol ER. Similar results were observed for the comparison of oxycodone CR and placebo (p <0.001).

Assessments that evaluated health status showed positive effects of tapentadol ER compared with placebo were consistent with the outcome of the efficacy assessments. For the change from baseline to endpoint in the EQ-5D health status index, the small numeric difference favoring tapentadol ER compared with placebo was statistically significant (p=0.020). Similar results were observed for the oxycodone CR group compared with placebo group at endpoint (p=0.019). The SF-36 Health Survey findings suggested that tapentadol ER has a more positive effect on health status than placebo in the domains expected to be affected in chronic LBP (i.e., "physical functioning", "role-physical", "bodily pain", and "vitality"). Positive effects on "role-physical" and "bodily pain" were observed in the comparison of oxycodone CR and placebo.

SAFETY RESULTS: The overall incidence of TEAEs was higher in the active-treatment groups (75.5% in the tapentadol ER group and 84.8% in the oxycodone CR group) than in the placebo group (59.6%). The most common adverse events in any treatment group were nausea, constipation, vomiting, headache, somnolence, dizziness, and pruritus, all of which were reported in a higher percentage of subjects in the active-treatment groups than in the placebo group. The incidence of nausea, constipation, dizziness, vomiting, insomnia, and pruritus was lower in the tapentadol ER group than in the oxycodone CR group. In particular, the incidence of vomiting, constipation, and pruritus with tapentadol ER (9.1%, 13.8%, and 7.2%, respectively) was less than half that reported with oxycodone CR (19.2%, 26.8%, and 16.8%, respectively).

No pattern for higher incidences of AEs with higher doses of study drug in the maintenance period was observed in the active-treatment groups, most probably due to the trial design, which involved titration to the optimal dose in terms of analgesia and tolerability within the protocol dose range for each subject.

There were no deaths during the study. More subjects in the active-treatment groups reported treatment-emergent serious adverse events (2.2% in the tapentadol ER group and 3.4% in the oxycodone CR group) than in the placebo group (0.9%). No individual serious adverse event was reported for more than 1 subject each in any treatment group. More subjects in the oxycodone CR group (31.7%) had TEAEs that led to study discontinuation than in the tapentadol ER (16.7%) and placebo group (4.4%). In particular, the percentage of subjects who discontinued treatment due to TEAEs of nausea, constipation, dizziness, vomiting, headache, and pruritus in the tapentadol ER group was less than one-half of that reported for subjects in the oxycodone CR group (1.6% vs. 11.3% for nausea, 1.3% vs. 4.3% for constipation, 2.2% vs. 6.4% for dizziness, 2.5% vs. 7.0% for vomiting, 0.3% vs. 2.7% for headache, and 0.3% vs. 3.7% for pruritus). In both active-treatment groups, nausea and vomiting was reported more often for female than male subjects, and constipation and dizziness were reported more often for subjects ≥65 years old than for subjects <65 years old.

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

PAC-SYM assessments indicated a clinically and statistically significant advantage for tapentadol ER over oxycodone CR for the overall score, the overall rectal subscale score, and overall stool subscale score (p-values ≤0.038). For subjects with TEAEs of constipation, the PAC-SYM overall score, the overall abdominal subscale score, and overall stool subscale score demonstrated statistically significant differences favoring tapentadol ER compared with oxycodone CR at endpoint (p-values ≤0.037).

The COWS score indicated a generally low degree of opioid withdrawal 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 100 mg to 250 mg b.i.d. was effective when administered in a controlled dose adjustment design for up to 15 weeks in subjects with moderate to severe chronic LBP. The efficacy results were more robust than oxycodone CR, reflective of the improved tolerability and reduced rate of discontinuation of subjects in the tapentadol ER group compared to oxycodone CR. The safety profile of tapentadol ER was consistent with the profile expected for centrally acting analgesics with mu-opioid activity, but consistently demonstrated improved gastrointestinal tolerability as expressed by reduced incidences of constipation, nausea, and vomiting, as well as reduced incidence of dizziness, insomnia, 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. No clinically important safety signals were evident with tapentadol ER compared with placebo. These results demonstrate that tapentadol ER 100 mg to 250 mg b.i.d. has analgesic efficacy with an improved tolerability profile in subjects with moderate to severe chronic LBP.

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