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(s)	Tapentadol HCl

Protocol No.: R331333-PAI-3007 (KF5503/24)

Title of Study: A One-Year, Randomized, Open-Label, Parallel-Arm, Phase 3 Long-Term Safety Study, With Controlled Adjustment of Dose, of Multiple Doses of Tapentadol Extended-Release (ER) and Oxycodone Controlled-Release (CR) in Subjects With Chronic Pain.

EudraCT Number: 2006-003482-14

Coordinating Investigator: [redacted] Detmold, Germany

Publication (Reference): None

Study Period: 14 November 2006 – 25 July 2008

Phase of Development: Phase 3

Objectives:

The primary objective of the study was the evaluation of the safety profile of tapentadol ER base at doses ranging between 100 mg and 250 mg twice-daily over long-term exposure of up to 1 year. The secondary objectives were the characterization of: 1) Tapentadol ER and oxycodone CR dose requirements during long-term exposure, 2) symptoms severity related to constipation using the Patient's Assessment of Constipation Symptom (PAC-SYM), 3) sleep quality by using Sleep Questionnaire (SQ), 4) opioid withdrawal following discontinuation of treatment using both the Clinical Opiate Withdrawal Scale (COWS) and, in the United States (US), the Subjective Opiate Withdrawal Scale (SOWS) questionnaires, 6) efficacy based on the Subject's and Investigator's Global Assessment of the study drug, 7) pain intensity scores over the 1-year study period, measured with an 11-point numerical rating scale (NRS), 8) efficacy based on Patient's Global Impression of Change (PGIC) using a 7-point verbal rating scale, 9) quality of life based on EuroQol-5 Dimension (EQ-5D), and 10) quality of life based on Short Form-36 Health Survey (SF-36).

Methods: This was a randomized, multicenter, open label, active control, parallel group, Phase 3 safety study of tapentadol ER or oxycodone CR in subjects with chronic pain. The doses of tapentadol ER investigated ranged from 100 mg to 250 mg twice daily (b.i.d.), the doses of active comparator oxycodone CR ranged from 20 mg to 50 mg b.i.d. Doses of tapentadol ER base 50 mg b.i.d. and oxycodone CR 10 mg b.i.d. were used for the purpose of titration only.

The study consisted of a screening phase (duration up to 14 days), a washout phase (duration 3 to 7 days), and an open-label active treatment phase with titration and maintenance (total duration 52 weeks). After completing the washout period, eligible subjects were randomized in a 4:1 ratio and received tapentadol ER 50 mg b.i.d. or oxycodone CR 10 mg b.i.d. for the first 3 days (6 consecutive doses). The dose was then increased to tapentadol ER 100 mg b.i.d. or oxycodone 20 mg b.i.d. (minimum required therapeutic dose) and subjects were to receive this dose for the next 4 days. This was the lowest dose of study drug allowed for the remainder of the study. The study medication (either tapentadol ER or oxycodone CR) was taken orally b.i.d. in the morning and in the evening. During the maintenance phase, upward titration occurred at a minimum of 3 day-intervals (6 consecutive doses) in increments of tapentadol ER 50 mg b.i.d. or

oxycodone 10 mg b.i.d. The maximum doses allowed were tapentadol ER 250 mg b.i.d. or oxycodone 50 mg b.i.d. Downward titration was permitted (but not below the minimum therapeutic dose) using the same decrements without a time restriction. Doses were assessed at the scheduled visits and adjustment made as necessary. A follow-up visit at the site was scheduled within 4 days following the last study medication dose intake. Additionally, a follow-up telephone call to record any adverse events was completed within 10 to 14 days following the last study medication dose intake.

Number of Subjects (planned and analyzed): The total number of subjects to be randomized for the study was 1075. The safety analysis set included 894 subjects in the tapentadol ER group and 223 subjects in the oxycodone CR group. A total of 876 subjects in the tapentadol ER group and 219 in the oxycodone CR group 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, had clinical diagnosis of knee or hip osteoarthritis (OA) with history of pain at the reference joint present at least for 3 months or clinical diagnosis of low back pain (LBP) of benign origin present for at least 3 months, were dissatisfied with their current analgesic therapy (e.g., non-steroidal anti-inflammatory drugs, [NSAIDs], cyclooxygenase-II [COX-II] inhibitors, opioids, paracetamol/acetaminophen, and had pain intensity ≥4 on NRS at baseline after washout).

Test Product, Dose and Mode of Administration, Batch No.: Tapentadol extended-release film-coated oral tablets in doses of 50 mg (Lot Nos. PD2395, PD2124, and PD2558), 100 mg (Lot Nos. PD2353, PD2127, PD2446, and PD2443), 150 mg (Lot Nos. PD2356 and PD2133), 200 mg (Lot Nos. PD2362 and PD2136) and 250 mg (Lot Nos. PD2371 and PD2139).

Reference Therapy, Dose and Mode of Administration, Batch No.: Oxycodone CR oral tablets in doses of 10 mg (Lot Nos. 7020281, 25157, 24998, and 26121), 20 mg (Lot Nos. 7020391, 25021, and 26125), and 40 mg (Lot Nos. 7020491 and 24857).

Duration of Treatment: The maximum duration of treatment was 52 weeks including 1-week titration.

Criteria for Evaluation:

Efficacy: Efficacy was assessed by pain intensity scores with an 11-point NRS, Patient's Global Impression of Change (PGIC), Global Assessment of study drug by subject and Investigator.

Safety: Safety assessment consisted of adverse event reporting, clinical laboratory tests, vital sign measurements (pulse rate, respiratory rate, blood pressure [supine or sitting]), physical examinations, electrocardiogram (ECG), Patient's Assessment of Constipation Symptoms (PAC-SYM), and opioid withdrawal using the COWS and SOWS.

Additional Patient-Reported Outcomes included Short Form-36 Health Survey (SF-36) scores, EuroQol-5 Dimension (EQ-5D) scores, and Sleep Questionnaire.

Pharmacokinetics**:** Blood samples were collected at specified visits.

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

Statistical Methods: All subjects who received at least 1 dose of study drug were included in the safety analysis set. All randomized subjects who received at least 1 dose of study drug were included in the ITT analysis set, with the exception of the 20 randomized and dosed subjects at Site 001023 in Clearwater (US) which had major site audit findings. The ITT analysis set was used to perform all efficacy analyses. The projected sample size was based on the minimum required number of 300 to 500 subjects exposed to tapentadol ER for at least 6 months and 100 subjects exposed for at least 12 months to support the regulatory submission. It was assumed that the discontinuation rate was 40% during the first month and 10% every month thereafter. This resulted in 35% of randomized subjects remaining at 6 months and 19% at 12 months. In order to meet the exposure requirement of tapentadol ER for both 6 months and 12 months, approximately 860 subjects were to be randomized to tapentadol ER. With 4:1 randomization

ratio, approximately 215 subjects were to be randomized to oxycodone CR. The planned total number of subjects to be randomized for the study was 1075.

A summary of the number and percentage of subjects in each analysis set were provided. All analysis summaries are displayed by treatment groups of tapentadol ER and oxycodone CR regardless of the doses individual subjects received during the treatment phase (unless otherwise stated).

In addition, summary tables with both treatment groups combined were presented for demographic and baseline characteristics, concomitant medication, medical history, physical examination, and disposition. Summary tables for continuous variables (descriptive statistics) included mean, standard deviation (SD), median, mode, N, and range. The summary tables for categorical variables included frequency counts and percentage of subjects. No formal hypothesis was formulated for this study. Demographic and baseline characteristics were summarized for the safety analysis set. Descriptive statistics are provided for continuous variables such as age, weight, height, body mass index (BMI) and baseline pain.

RESULTS:

STUDY DRUG EXPOSURE:

A total of 1121 subjects were randomized to receive tapentadol ER (896 subjects) or oxycodone CR (225 subjects). In addition, 2 subjects (1 in tapentadol ER, 1 in oxycodone CR) were not randomized in error but received study medication. All subjects who received at least 1 dose of study drug were included in the safety analysis set (894 subjects on tapentadol ER and 223 subjects on oxycodone CR). Three randomized subjects in each group did not receive study medication.

Approximately 57% of subjects were female. The majority of subjects were white (89.1%) and under 65 years of age (72.1%).

More subjects in the safety analysis set completed the treatment period in the tapentadol ER group (46.2%) than in the oxycodone CR group (35.0%). The most common reason for treatment discontinuation for both treatment groups was adverse event (22.7% in the tapentadol ER group and 36.8% in the oxycodone CR group). The percentage of subjects who discontinued due to lack of efficacy was higher in the tapentadol ER group (8.1%) than in the oxycodone CR group (3.1%).

The median duration of treatment was 268 days (38.3 weeks) in the tapentadol ER group and 59 days (8.4 weeks) in the oxycodone CR group. A total of 487 (54.5%) tapentadol ER subjects and 92 (41.1%) oxycodone CR subjects took study medications for at least 6 months. A total of 227 (25%) of tapentadol ER subjects and 44 (20%) of oxycodone CR subjects took study medications for at least 1 year.

The mean total daily dose was 326.7 mg for tapentadol ER and 51.5 mg for oxycodone CR.

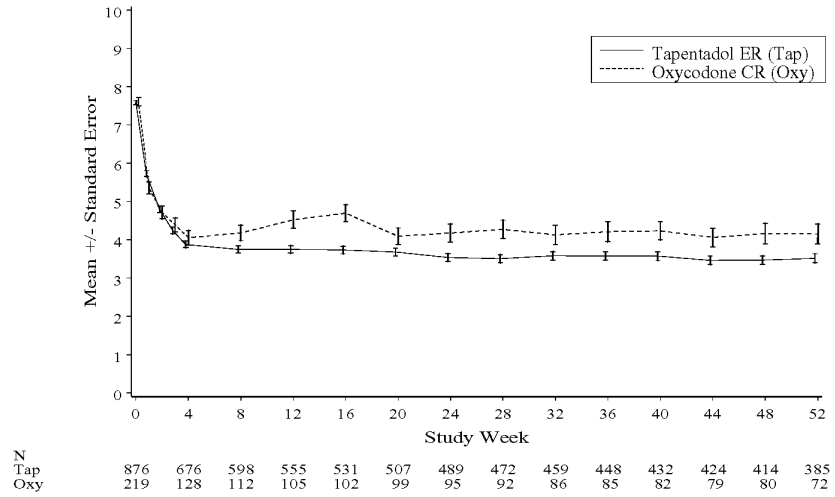
For each individual, the longest number of consecutive days at the high dose (defined as ≥400 mg/day for tapentadol ER and ≥80 mg/day for oxycodone CR) was calculated. The mean number of days for the longest number of consecutive days was 116 days in the tapentadol ER group and 77 days in the oxycodone CR group.

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. Mean baseline pain intensity scores were 7.58 for the tapentadol ER group and 7.61 for the oxycodone CR group. Up until 4 weeks after first dose, the mean pain intensity scores were similar in both treatment groups. From that point onward, mean pain intensity scores were consistently lower in the tapentadol ER group than in the oxycodone CR group (Figure 1). Pain intensity scores decreased over time for both treatments, with mean scores at end point of 4.37 and 4.52 for the tapentadol ER and oxycodone CR groups, respectively.

Figure 1: Pain Intensity Score over Time (ITT Analysis Set)



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 and oxycodone CR in this population.

Patient and Investigator Global Assessment of Study Drug

Overall, both subjects and investigators had a positive perception of the study drug at the end of the study. The majority of subjects reported a Global Assessment of 'Excellent', 'Very Good', or 'Good' at end point (75.1% and 72.3% for tapentadol ER and oxycodone CR, respectively). Similarly, the majority of investigators reported a Global Assessment of 'Excellent', 'Very Good', or 'Good' at end point (77.3% and 72.3% for tapentadol ER and oxycodone CR, respectively). These results were consistent throughout the study.

Patient's Global Impression of Change (PGIC)

Overall, subjects had a positive Global Impression of Change at the end of the study. The percentages of subjects reporting each category were similar in both treatment groups at end point. A change of 'Very Much Improved' or 'Much Improved' was reported by 48.2% of subjects for tapentadol ER and 41.3% of subjects for oxycodone CR. For both groups, the most frequently reported change for the PGIC at end point was 'Much Improved'.

Time to Treatment Discontinuation Due to Lack of Efficacy

Subjects randomized to tapentadol ER discontinued due to lack of efficacy earlier than those in the oxycodone CR group. The rate of discontinuation due to lack of efficacy decreased after Week 8 for subjects in the tapentadol ER group and after Week 4 for subjects in the oxycodone CR group. After 4 weeks, 2.8% (25 of 894 subjects) of the tapentadol ER group and <1.0% (2 of 223 subjects) of the oxycodone CR group discontinued due to lack of efficacy and after 8 weeks 4.9% (44 of 894 subjects) of the tapentadol ER group and 1.3% (3 of 223 subjects) of the oxycodone CR group discontinued due to lack of efficacy.

Additional Patient-Reported Outcomes

SF-36 Health Survey: Both treatments improved the subjects' physical, social, and mental well being. Improvements were observed in both treatments over all parameters; however, a slightly greater improvement was noted in the tapentadol ER group.

EuroQoL-5 Dimension Questionnaire: In both treatment groups, there were numerical increases in the percentages of subjects reporting having no problems for each of the 5 dimensions (mobility, self-care, usual activities, anxiety/depression, and pain/discomfort) at end point. Mean changes from baseline over time were small for all 5 dimensions in both treatment groups.

Sleep Questionnaire: Overall, no noteworthy changes were observed in the 2 treatment groups for all 4 items of the Sleep Questionnaire.

Pharmacokinetic Results

Pharmacokinetic (PK) results will be reported separately. No PK/PD relationships were analyzed.

Efficacy Conclusions

Although efficacy was not a primary objective of this study, pain intensity was assessed at every visit. More reduction of pain intensity scores (based on NRS) was observed from Week 4 and throughout the duration of the study in the tapentadol ER group than in the oxycodone CR group.

A higher percentage of subjects in the tapentadol ER group reported 'Very Much Improved' and 'Much Improved' on the PGIC than in the oxycodone CR group at the end of the study. In both groups, the most frequently reported PGIC assessment at end point was 'Much Improved'.

Based on the Patient and Investigator Global Assessment of study drug, tapentadol ER was rated as 'Excellent' or 'Very Good' by a proportionally greater number of subjects and investigators.

SAFETY RESULTS:

Overall, tapentadol ER was well tolerated across the studied dose range with the overall safety profile very similar to the profiles reported in the previous studies with tapentadol ER and IR. There were no unexpected safety findings among adverse events, laboratory values, vital signs, or ECGs. No deaths were reported during the study.

Serious adverse events (SAEs) were reported in 5.5% (49) subjects in the tapentadol ER group and 4.0% (9) subjects in the oxycodone CR group. Cardiac SAEs reported during tapentadol ER treatment were in subjects who were known to have had underlying cardiovascular conditions, including angina pectoris in 1 subject, CABG x3 (Coronary artery bypass graft on 3 vessels) for coronary artery disease in 1 subject, and atrial fibrillation in 1 subject. These SAEs were considered by the investigator to be not related to study drug.

The overall incidence of treatment-emergent adverse events (TEAEs) was lower in the tapentadol ER group (85.7%) than in the oxycodone CR group (90.6%). The most common TEAEs were constipation (22.6% vs 38.6%), nausea (18.1% vs 33.2%), dizziness (14.8% vs 19.3%), somnolence (14.9% vs 11.2%), headache (13.3% vs 7.6%), vomiting (7.0% vs 13.5%), fatigue (9.7% vs 10.3%), pruritus (5.4% vs 10.3%).

A similar percentage of subjects who took low dose tapentadol ER (<200 mg b.i.d.) or high dose tapentadol ER (≥200 mg b.i.d.) reported TEAEs (85.0% and 87.2% respectively). Slightly more TEAEs were experienced by subjects who took high dose oxycodone CR (≥40 b.i.d.) than low dose oxycodone CR (<40 mg b.i.d.) (95.6% and 89.3%, respectively). Constipation incidence followed the same trend; constipation was experienced by a similar percentage of subjects in the tapentadol low and high dose groups (21.9% and 24.0% respectively), but constipation was reported by more subjects in both high and low dose oxycodone CR treatments (51.1% and 35.4% respectively).

The rate of rise in the percent of subjects who discontinued due to TEAEs was rapid in the oxycodone CR group and continued more slowly from Week 4 throughout the study. The percentage of subjects who discontinued due to TEAEs in the tapentadol ER group increased at a slower rate during the first 4 weeks than in the oxycodone CR group. Beyond week 4, the discontinuation rate was slower and similar in both treatment groups. More subjects in the oxycodone CR treatment group (36.8%) had treatment-emergent adverse events that led to study discontinuation than subjects in the tapentadol ER group (22.1%). The most common adverse events that led to study discontinuation were nausea, vomiting, constipation and dizziness.

The rate of rise of the percentage of subjects with a first event of nausea and a first event of constipation was faster in the oxycodone CR group and continued at a much slower rate until study completion. The same was noted for subjects with a first event of vomiting, in that the first events occurred earlier, with a higher incidence in the oxycodone CR group and began to plateau around Week 4.

Three subjects each in the tapentadol ER group had TEAEs of increased blood creatine phosphokinase and GGT during the study. Blood creatine phosphokinase was also increased in 1 subject in the oxycodone CR group. Two subjects each in the tapentadol ER group experienced increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glucose, triglycerides, hepatic enzymes, and lipase. These events were isolated and no drug-related relationship could be concluded from these observations.

The mean PAC-SYM overall score at baseline was 0.5 (i.e., absent to mild) in each treatment group. At endpoint, the mean changes from baseline in the overall score were lower in the tapentadol ER group (0.1) than in the oxycodone CR group (0.3), indicating more severity in the oxycodone CR group. For all 3 of the PAC-SYM subscales, the mean changes from baseline were lower for the tapentadol ER groups than in the oxycodone CR group.

The incidence of potentially clinically important vital signs was similar between treatment groups. No obvious pattern of clinically relevant changes across treatment groups in mean values over time for pulse rate, systolic blood pressure, diastolic blood pressure, and respiration rate were noted.

Clinically meaningful changes in the overall ECG interpretation from baseline to endpoint as assessed by the investigators were reported for 4 (0.5%) subjects in the tapentadol ER group and no subjects in the oxycodone CR group. None of these events was considered an SAE and 3 subjects completed the study. Subject [redacted] withdrew on Day 16 due to a non treatment-emergent AE that occurred at screening (increase in QTcB). At endpoint, the majority of subjects (>50%) in each treatment group had ECGs that were normal as assessed by the central reviewer. The percentage of subjects with an overall interpretation of "abnormal, clinically significant" was similar between treatments (36.8% in the tapentadol ER group and 34.5% in the oxycodone CR group) at end point. No QT or QTc abnormalities were detected in the oxycodone CR group and <1% of subjects experienced QT or QTc abnormalities in the tapentadol ER group. None of the interval values that met the potentially clinically important criteria was reported as a TEAE.

Clinical Opiate Withdrawal Scale (COWS)

The number of subjects with a COWS assessment and who were not taking opioids was 296 on tapentadol ER and 73 on oxycodone CR. All subjects either had no opioid withdrawal or opioid withdrawal of mild or moderate intensity. Among subjects who had COWS assessment within 2 to 4 days after discontinuation of study medication and did not receive any opioids, 77.6% of tapentadol ER subjects and 72.7% of the oxycodone CR subjects had no opioid withdrawal. Opioid withdrawal of mild or moderate intensity was observed in 17.6% and 4.8%, respectively, in the tapentadol ER group and in 22.7% and 4.5%, respectively, in the oxycodone CR group. Among subjects who had COWS assessment at least 5 days after study medication and did not receive any opioids, 88% of tapentadol ER subjects and 84% of the oxycodone CR subjects had no opioid withdrawal. Opioid withdrawal of mild or moderate intensity was observed in 10.8% and 1.2%, respectively, in the tapentadol ER group and in 14.0% and 2.0%, respectively, in the oxycodone CR group.

Subjective Opiate Withdrawal Scale (SOWS)

The level of opioid withdrawal perception by the subjects at treatment discontinuation was similar in the tapentadol ER group and oxycodone CR group. Both COWS and SOWS indicated low physical dependence in both groups.

Safety Conclusions

- Overall, tapentadol ER was well tolerated across the reported dose range and the overall safety profile was very similar in pattern to what has been observed in the previous studies with tapentadol ER and IR. There were no unexpected safety findings among adverse events, laboratory values, vital signs, or ECGs.
- The total incidence of treatment-emergent AEs in the tapentadol ER treatment group was lower than in the oxycodone CR group and was consistent with previous tapentadol ER and IR studies. The incidence of AEs leading to discontinuation in the tapentadol ER group was lower than in the oxycodone CR group (22.1% and 36.8%, respectively).
- The tapentadol ER group showed an improved GI profile and a reduced incidence of pruritus than the oxycodone CR group and confirmed the results of previous studies.
- The incidence of SAEs was very low and similarly distributed in both treatment groups.
- No deaths were reported during the study.
- More than 70% of subjects who did not take opioid medication after study drug discontinuation did not experience any opioid withdrawal as measured by the COWS, The numbers of moderate opioid withdrawal were in general low in both treatment groups, indicating low physical dependence overall. The subjective perception of opioid withdrawal with the SOWS questionnaire confirmed the COWS results.

CONCLUSION:

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 long-term period. No clinically important safety signals were evident with tapentadol ER compared with oxycodone CR.