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-3009 (KF5503/12)

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 (OA) of the Knee

EudraCT Number: 2006-005783-67

Coordinating Investigator: [redacted]

Publication (Reference): None

Study Period: 04 June 2007 to 18 July 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 of 100 to 250 mg twice daily (b.i.d.) in subjects with moderate to severe chronic pain from 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 active 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 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. The use of paracetamol/acetaminophen was prohibited, with the exception of intermittent use with total daily doses of up to 1000 mg for no more than 3 consecutive days for reasons other than the study-related chronic pain. The starting doses in the titration period 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 received this dose for the next 4 days. Thereafter, during both 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 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.

Number of Subjects (planned and analyzed): Planned: 942 subjects (314 per treatment group); randomized: 990 subjects; analyzed for safety (safety analysis set): 987 subjects; analyzed for efficacy: full analysis set (ITT): 987 subjects; and per-protocol analysis set: 876 subjects; analyzed for tapentadol serum concentrations: 1294 samples.

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

Test Product, Dose and Mode of Administration, Batch No.: Tapentadol ER film-coated oral tablets in doses of 50 mg (Lot FFIR29, FFIR30, FFIR31, FFIR32, FFIR39, GAIR49, GAIR50), 100 mg (Lot FKEG50, FKEG51, GAEG58, GAEG59), 150 mg (Lot FGNK18, FGNK20, GANK28, GBNK30), 200 mg (Lot FHGU60, GBGU63).

Reference Therapy, Dose and Mode of Administration, Batch No.: Oxycodone CR (OxyContin®) overencapsulated oral tablets in doses of 10 mg (Lot E04565-076E01), 20 mg (Lot E04565-078E01, E04565-123E01), 30 mg (Lot E04565-079E01), 40 mg (Lot E04565-081E01).

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 FISS07, FISS08, FISS09, FISS10, FISS11, FISS12, FISS13, FISS14, FISS15, FISS16, FISS17, FISS18, FISS19, FISS20, FISS21 and oxycodone CR placebo had Lot E04565-087E01.

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 b.i.d. pain intensity assessments (11-point NRS), response rates based on the 11-point NRS, 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 study drug did not sufficiently reduce pain), EuroQol-5 Dimension Health Questionnaire (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, and blood pressure [supine or sitting]), clinical laboratory values, 12-lead ECG, and Clinical Opioid Withdrawal Scale (COWS).

Pharmacokinetics**:** Blood samples were collected at visits specified in the protocol to obtain population pharmacokinetic data.

Statistical Methods:

Efficacy: The primary analysis was performed on the full analysis set (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 U.S. 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-U.S. 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 the placebo group in the primary endpoint. The alternative hypothesis was that the tapentadol ER group was different from the placebo group in the primary endpoint. The primary efficacy analysis 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. The p value for the treatment difference along with the 2-sided 95% CI were presented. The primary imputation method was the last observation carried forward (LOCF). Sensitivity analyses were performed with various imputation methods (baseline observation carried forward [BOCF] and 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: 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 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 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 to 3 were provided by week and endpoint. A frequency distribution of responses to the number of awakenings (Item 2) and sleep quality (Item 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 same ANCOVA model used for the primary efficacy analysis was used to analyze the primary endpoint by baseline pain intensity category. Analysis of the primary efficacy endpoint for the per-protocol analysis set was performed as an exploratory analysis.

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

Safety: Descriptive statistics and frequency counts (percentage of subjects) were used to assess safety variables, including adverse events, laboratory results, vital signs, and ECG assessments. Treatment comparisons for the change from baseline were assessed. Odds ratios and corresponding 95% CIs were generated for the occurrence of nausea, vomiting, and constipation. The distributions of time to first occurrence of nausea, vomiting, or constipation and time to discontinuation of treatment due to adverse

events were presented with Kaplan-Meier estimates, and pairwise comparisons were performed using the log-rank test. Opiate withdrawal effects were assessed using descriptive statistics of the COWS scores. Treatment comparisons for COWS 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: The percentage of subjects completing double-blind treatment was greater in the placebo (65.6%) and tapentadol ER (58.3%) groups than in the oxycodone CR group (36.6%). The most common reasons for study discontinuation in the active-treatment groups were adverse events followed by subject choice (subject withdrew consent). The percentage of subjects who discontinued treatment due to adverse events was greater in the oxycodone CR group (42.6%) than in the tapentadol ER (18.8%) or placebo (8.3%) groups.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: Demographic and baseline characteristics were comparable across the treatment groups. A majority of subjects were female (71.6%), white (99.3%), and younger than 65 years of age (60.7%). In addition, most subjects had not taken opioids during the 3 months prior to the screening visit (84.3%) and were categorized as having severe baseline pain intensity (NRS ≥ 6, 88.9%).

EXTENT OF 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: 105.0, 104.0, and 35.0 days, respectively). During the titration period, the median of the modal total daily dose (TDD) was 200 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 TDD was 300 mg for tapentadol ER and 40 mg for oxycodone CR.

The median duration of treatment during the maintenance period was comparable among the 3 groups (12 weeks). The median percentage of time on the modal dose during the 12-week maintenance period was >97% in all 3 treatment groups. More subjects in the tapentadol ER (48.8%) and placebo (63.8%) groups than in the oxycodone CR group (31.7%) received a high dose (i.e., TDD of ≥400 mg for tapentadol ER and ≥80 mg for oxycodone CR) at least once during the maintenance period.

PHARMACOKINETICS: A total number of 1294 samples were analyzed for tapentadol serum concentrations. Within the intended tapentadol ER dose range of 100 to 250 mg b.i.d., mean tapentadol serum concentrations increased with dose. Furthermore, quite stable tapentadol serum concentrations were observed across the 12-week maintenance period for the tapentadol ER dose levels of 100, 150, and 200 mg b.i.d.). For the tapentadol ER dose of 250 mg b.i.d., a somewhat lower mean concentration was observed at the final sampling time during the maintenance period, possibly the result of the generally longer interval between dosing and PK sampling at that visit for the subjects receiving that dose.

EFFICACY RESULTS: For the change from baseline in the average pain intensity at Week 12 of the maintenance period (primary efficacy variable for the U.S. regulatory authority) and the change from baseline in the average pain intensity over the 12-week maintenance period (primary efficacy variable for non-U.S. regulatory authorities), the reductions in pain intensity were numerically larger in the tapentadol ER group than in the placebo group and numerically smaller in the oxycodone CR group than in the placebo group. Tapentadol ER failed to show a statistically significant reduction compared with placebo using LOCF (both p values ≥0.135). The comparison between oxycodone CR and placebo likewise failed to demonstrate a statistically significant reduction in average pain intensity for either endpoint (both p values ≥0.279). Therefore, the study did not demonstrate assay sensitivity.

Sensitivity analyses were performed on the primary efficacy endpoint using BOCF, WOCF, PMI, and modified BOCF imputation methods. Neither active treatment was statistically superior to placebo using any of these imputation methods.

For the comparison of tapentadol ER and placebo, subjects with moderate baseline pain (LS mean difference of -0.7 for both endpoints) showed greater improvement than subjects with severe baseline pain (LS mean difference of -0.2 for both endpoints). However, the differences were not statistically significant. For the comparison of oxycodone CR and placebo, the direction of the difference indicated more pain relief in the placebo group, which was more pronounced in the subgroup of subjects with moderate baseline pain. Subjects who had not taken prior opioid medications had greater numerical improvement in pain intensity scores than subjects who had taken prior opioids both at Week 12 and for the overall maintenance period in the tapentadol ER group. In the oxycodone CR group, subjects who had not taken prior opioid medications had lower numerical improvement in pain intensity scores than subjects who had taken prior opioids.

There were no significant differences between the 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. In contrast, placebo was superior to oxycodone CR for the proportion of subjects showing at least 30% improvement in pain intensity ($p<0.001$).

There was a statistically significant difference between each active-treatment group and placebo in time to treatment discontinuation due to lack of efficacy ($p\leq0.027$). There was a statistically significant advantage for tapentadol ER over placebo in PGIC scores at the end of treatment ("much improved" or "very much improved" was reported by 56.0% [139/248] and 43.2% [127/294] of the subjects, respectively) ($p=0.015$) when 71 tapentadol ER-treated subjects and 43 placebo-treated subjects who had the assessment obtained more than 1 day after the end of treatment were not included in the analysis. The active treatment groups were numerically better than placebo for the WOMAC global score and for subscales of pain, stiffness, and physical function throughout the maintenance period, but the differences were not consistently statistically significant at all time points.

For the sleep questionnaire 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 was significantly different from placebo. There were no statistically significant differences favoring tapentadol ER over placebo for the SF-36 Health Survey results or the EQ-5D health status index.

SAFETY RESULTS: The overall incidence of TEAEs was higher in the oxycodone CR group (84.9%) than the tapentadol ER (67.1%) and placebo (55.5%) groups. The adverse events that occurred in ≥10% of the subjects in either active-treatment group were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The incidence was lower in the tapentadol ER group than the oxycodone CR group for nausea (20.4% vs. 37.5%), constipation (17.9% vs. 35.0%), vomiting (10.3% vs. 26.0%), dizziness (21.9% vs. 26.9%), and pruritus (1.3% vs. 10.9%).

More subjects in the oxycodone CR group (3.9%) reported serious adverse events compared with the tapentadol ER (0.6%) and placebo (1.2%) groups. More subjects in the oxycodone CR group (42.3%) had TEAEs that led to study discontinuation than in the tapentadol ER (18.8%) or placebo (8.0%) groups. The majority of TEAEs that led to study discontinuation in the oxycodone CR group were from the gastrointestinal disorders SOC (28.7%, compared with 11.6% in the tapentadol ER group) and dizziness (11.5%, compared with 4.7% in the tapentadol ER group).

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 with 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.

The COWS score indicated a generally low degree of opioid withdrawal following abrupt discontinuation of treatment, with most subjects (80.4% in the tapentadol ER group and 79.4% in the oxycodone CR group)

who did not take opioids after study drug discontinuation having no withdrawal on Days ≥2 to <5 after the last study drug intake. Among the small number of subjects who took opioids after study drug discontinuation, 75.0% (3/4) in the tapentadol ER group and 57.1% (4/7) in the oxycodone CR group had no withdrawal on Days ≥2 to <5 after the last study drug intake. All remaining assessed subjects had mild or moderate withdrawal.

CONCLUSION: Statistically significant improvements in pain intensity were not demonstrated in this study when tapentadol ER 100 to 250 mg b.i.d. was administered in a controlled dose-adjustment design for up to 15 weeks to subjects with moderate to severe chronic OA of the knee. There were, however, numerically greater decreases from baseline in pain intensity with tapentadol ER than placebo. The direction of the effect on pain intensity in this study is consistent with the numerically greater and statistically significant tapentadol ER effects in 2 Phase 3 studies of identical design, 1 in subjects with chronic lower back pain and 1 in subjects with chronic pain due to OA of the knee. The safety profile of tapentadol ER was consistent with the profile expected for a centrally acting analgesic with mu-opioid agonist effects but with a reduced incidence of constipation, nausea, vomiting, dizziness, and pruritus compared with oxycodone CR 20 to 50 mg b.i.d. and a reduced incidence of adverse events leading to discontinuation of treatment. The increased overall tolerability of tapentadol ER compared with oxycodone CR, which was seen in this and other trials, 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 are consistent with results from other studies indicating that tapentadol ER has a favorable tolerability profile in subjects with moderate to severe chronic OA of the knee.

ICTR SYNOPSIS SUPPLEMENT

R3 31333-PAI-3009 (J&JPRD)
KF5503/12 (GRÜNENTHAL)

Original ICTR issue date:	27 Feb 2009	**DMS version:**	3.0
ICTR synopsis supplement date:	11 Mar 2015	**DMS version:**	1.0

1 SUPPLEMENT CONTENT

This document contains information about the trial that is not already covered in the synopsis of the corresponding clinical trial report.

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There were 2 amendments to the protocol.

Amendment 1 (22 Jun 2007) had the following important changes:

- Restrictions to analgesic medications starting at Visit V2 with the washout period were clarified.
- The prescription of analgesics allowed after completion of, or withdrawal from, trial treatment was clarified.
- Clarification of restriction of previous oral steroids to regular use was made.
- Follow-up Visit F2 was explicitly mentioned as required for discontinued subjects.
- Optional Visit V2 was changed to a necessary Visit V2 (phone or site visit).
- Subject duration for the study was corrected from 21 to 20 weeks and appropriate changes made throughout the protocol.
- With regards to PK properties, the CG5503 mg base was corrected from 21.5 to 86 mg and its salt from 25 to 100 mg in the PK sections and other relevant sections. The t_{max} for the IR formulation of 1.5 hours was added.
- AUC of tapentadol-O-glucuronide was corrected.
- Under Identity of Investigational Medicinal Product and Additional Analgesic Medication, Section 10.1.1, salt 291 mg and its free base of 250 mg was deleted because this tablet strength was not used in the trial.
- Under Identification of Treatment Allocation in Emergency, Section 10.1.7, Interactive voice response system (IVRS)/interactive web response system was changed to IVRS only.
- In the Information Sheet/Consent Form, to test for pregnancy, “blood” was changed to “urine” to test if the female was pregnant, and for double barrier method, the example of spermicidal cream plus diaphragm was omitted.
- For WOMAC questionnaire, Page 3 was inserted for questions 8 to 13.

In addition, textual and grammatical changes were made wherever appropriate throughout the protocol.

Amendment 2 (25 February 2008) had the following changes:

The definition of the full analysis set was modified to conform to an agreement reached with the Food and Drug Administration (FDA).

- A reference about instructing the subject on the use of the diary in the follow-up period was removed from Section 9.4.7 in the protocol as the diary was not used then.

The first and second amendments to the protocol were adopted while enrollment for the trial was ongoing. Following Amendment 1 currently active subjects had to sign the amended version of the consent form.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was not subjected to a clinical hold or early termination.

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

The names of principal investigators for all initiated sites (irrespective of whether they enrolled subjects or not) are not here listed because consent for public disclosure was not obtained.

Investigator	Site address
(Name not given, since no consent given)	London, HA3 7LT, UK
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