CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Grünenthal GmbH / Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	not available	
Name of Active Ingredient(s)	Tapentadol	

Protocol No.: R331333-PAI-3003 (KF5503/32), CR011215

Title of Study: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Doses of CG5503 Immediate-Release Formulation in the Treatment of Acute Pain from Bunionectomy Followed by a Voluntary Open-Label Extension

Coordinating Investigator: No coordinating investigator was assigned. Five investigators were involved in this study.

Publication (Reference): none

Study Period: 02 August 2006 to 23 May 2007 | **Phase of Development:** 3

Objectives: The primary objective of this study was to determine the efficacy of tapentadol immediate release (IR) using the sum of pain intensity difference (SPID) over 48 hours compared with placebo and to assess the safety and tolerability of repeated doses of tapentadol IR over the double-blind treatment period in subjects with acute pain following bunionectomy. The null hypothesis was that all tapentadol IR dosage efficacy results are equal to placebo, based on the mean $SPID_{48}$. The alternative hypothesis was that at least 1 tapentadol IR dosage is different from placebo (i.e., has a mean $SPID_{48}$ different from that observed for subjects receiving placebo).

Secondary objectives included the evaluation of the following parameters across treatment groups: a) comparison of the effect of tapentadol IR on the time to the first intake of rescue pain medication during the double-blind treatment period, b) evaluation of the effect of tapentadol IR versus placebo using the distribution of responder rates at each time point (i.e., at 12, 24, 48, and 72 hours) during the double-blind treatment period, c) evaluation of the efficacy of tapentadol IR by examining the total effect on pain intensity and pain relief over the 72-hour double-blind treatment period, d) evaluation of times from the initial dose to onset of perceptible pain relief and of meaningful pain relief measured by a double-stopwatch method, e) assessment of the Patient Global Impression of Change (PGIC) at the end of the double-blind treatment period, f) evaluation of the adverse event rates for nausea and vomiting across treatment groups in the double-blind treatment period, g) evaluation of tapentadol IR pharmacokinetics using the population pharmacokinetic approach in this study population (population pharmacokinetics will be reported separately), h) evaluation of the safety profile of tapentadol IR beyond 3 days in subjects who participated in the open-label extension period, and i) exploration of the efficacy of oxycodone HCl IR in comparison with tapentadol IR and with placebo.

Methodology: This was a multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled study of 3 doses of tapentadol IR (50, 75, and 100 mg) for postoperative pain following a bunionectomy, that was followed by an optional open-label extension period. The active comparator was oxycodone HCl IR 15 mg. The study consisted of 5 periods: screening (2 to 28 days before surgery), surgical (Day −1), qualification (Day 1, starting at the termination of postsurgical popliteal sciatic block or systemic analgesia and ending at qualification/randomization or after 9 hours), double-blind treatment (Days 1 to 3; 72 hours following randomization), and open-label extension (4 to 13 days after randomization with a safety follow-up that was 13 to 18 days after randomization). Subjects qualified to enter the study if their pain reached ≥4 on the 11-point numerical rating scale (NRS) no earlier than 10 hours after the first surgical incision and no more than 9 hours after termination of postoperative continuous popliteal sciatic block or systemic analgesia. Subjects were randomized within 30 minutes of the qualifying pain score. Pharmacokinetics, pharmacogenomics, efficacy, and safety were assessed during the double-blind treatment period. Subjects who completed the double-blind treatment period had the option to continue in the open-label extension period, during which only safety was assessed.

Number of Subjects (planned and analyzed): Planned: 600 (120/group); analyzed for efficacy (intent-to-treat analysis set): 602 subjects; analyzed for safety (safety set, double-blind period): 602 subjects; analyzed for safety (open-label extension): 405 subjects.

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Diagnosis and Main Criteria for Inclusion: Study subjects were men and nonpregnant, nonlactating women at least 18 and no more than 80 years of age, inclusive, with moderate to severe pain (≥4 on the 11-point NRS) that occurred within 9 hours after termination of noninvestigational postoperative analgesia that was administered following a bunionectomy that occurred at least 10 hours prior to qualification.

Test Product, Dose and Mode of Administration, Batch No.: Double-blind treatment period: Overencapsulated tablets containing 50, 75, or 100 mg tapentadol IR. Batch numbers: PD-2025, PD-2026, and PD-2027, respectively. Capsules were orally administered. The HCl salt form of the drug substance was used, but the doses are expressed as the free base.

Open-label extension period: 50-mg tablets of tapentadol IR. Batch number: PD-2021. Either 1 or 2 tablets (i.e., 50 or 100 mg tapentadol IR) were taken orally as needed.

Reference Therapy, Dose and Mode of Administration, Batch No.: Double-blind treatment period: Overencapsulated tablets matching those for tapentadol IR and containing placebo (batch PD-1959) or oxycodone HCl IR 15 mg (batch PD-2116). Capsules were orally administered. No reference therapy was administered during the open-label extension period.

Duration of Treatment: Double-blind study drug was administered as a single capsule, once every 4 to 6 hours over the 72 hours following randomization. Only on Day 1, subjects were allowed to take their second dose of study drug as soon as 1 hour and no later than 6 hours after the first dose.

During the open-label period, study drug was to be taken as 1 or 2 50-mg tablets (i.e., 50 or 100 mg tapentadol IR) every 4 to 6 hours, as needed for pain, over the 9 days following the double-blind treatment period.

Criteria for Evaluation:

Pharmacokinetics: Venous blood samples were collected via an indwelling catheter at 4 time points during the study: approximately 1 and 3 hours after the first dose of study treatment (Day 1) and before (predose) and approximately 2 hours after the third dose on Day 2 to determine serum tapentadol and oxycodone concentrations. Samples from placebo-treated subjects were not analyzed. The quantification of 2 oxycodone metabolites (noroxycodone and oxymorphone) was performed.

Efficacy: SPID at 48 hours relative to the first dose of study drug was the primary efficacy variable, (i.e., the cumulative effects of drug exposure on pain intensity over the first 48 hours of the 72-hour double-blind treatment period). Secondary variables were used to assess changes in pain intensity, the total effect, response rates, duration of effect, and subject's impression of overall response to the dosing regimen. Pain scale variables included: a) SPID at other time points (12, 24, and 72 hours after the first dose) and b) total pain relief (TOTPAR) and the sum of TOTPAR and SPID (SPRID) at each observation time point (12, 24, 48, and 72 hours after the first dose). Response rates were evaluated as the distribution of responder rates at 12, 24, 48, and 72 hours, with the response based on the percent change from baseline in pain intensity. Duration of effect was determined based on the time to use of rescue medication. The Patient Global Impression of Change (PGIC) in pain was assessed at the end of the double-blind treatment period. Also evaluated were the times from the initial dose to the onset of perceptible pain relief, of meaningful pain relief, and of confirmed perceptible pain relief. The evaluation of the time to confirmed perceptible pain relief included subjects who experienced both perceptible and meaningful pain relief within 12 hours after the first dose of study drug, and is recognized as an indicator of first onset of analgesia.

Safety: Safety and tolerability assessments were based on spontaneously reported adverse events and clinical laboratory tests, vital signs (pulse rate, temperature, blood pressure, and respiratory rate), SpO_2 (pulse oximetry), 12-lead electrocardiograms, and physical examination.

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

Pharmacogenomics: Blood samples were taken after the first study drug administration to allow for analysis of genes relevant to tapentadol or pain that may influence pharmacokinetics, efficacy, safety, or tolerability. The *CYP2D6*, *CYP3A4* and *CYP3A5* genes were genotyped as part of an exploratory study.

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Statistical Methods:

Pharmacokinetics: Serum concentrations as a function of time were explored for tapentadol and for oxycodone and its metabolites, noroxycodone and oxymorphone.

Efficacy: The primary efficacy analysis on the primary endpoint ($SPID_{48}$ with last observation carried forward [LOCF] versus placebo) was an analysis of covariance (ANCOVA) with treatment and investigator as factors and baseline pain intensity score as a covariate. The Hochberg procedure was applied to adjust p-values for multiple comparisons for all tapentadol IR groups versus placebo group. All pair-wise treatment differences were estimated based on the least-square means of the difference. Additional analyses included analyses by subgroup (i.e., sex, race, age, baseline pain, and time to second dose [early dose if <3 hours after first dose]), analyses using alternate imputation methods (i.e., baseline observation carried forward [BOCF] and worst observation carried forward [WOCF]), and comparisons with oxycodone.

The intent-to-treat (ITT) analysis set was used for the efficacy analyses and included all randomized subjects who received at least 1 dose of study drug after randomization and who had a valid baseline pain assessment.

Safety: Descriptive statistics and frequency analysis (percentage of subjects) were used to assess safety.

For the double-blind treatment period, the safety analysis set included all randomized subjects who received at least 1 dose of study drug. For the open-label treatment period, all subjects who received at least 1 dose of open-label study drug were included.

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

Pharmacogenomics: No exploratory genetic association analyses between genotypes in the CYP2D6, CYP3A4 and CYP3A5 genes and relevant clinical endpoints were performed at the time of this report. Future analyses will be reported separately.

SUMMARY - CONCLUSIONS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

The demographic and baseline characteristics were comparable across the treatment groups in the double-blind period. A majority of subjects had severe pain at baseline (148 subjects and 454 subjects with moderate or severe baseline pain, respectively). The 602 treated subjects were primarily women (87%) and <65 years of age (94%). The median overall age was 46 years (range of 18 to 77 years). Most subjects were white (55%), black (20%), or Hispanic (22%).

Of the 459 subjects who completed the double-blind period, 428 subjects (93%) entered the open-label period. In the open-label period, most subjects were women (87%) and <65 years of age (84%). The median overall age was 48 years (range of 18 to 74 years). Most subjects were white (55%), black (19%), or Hispanic (24%).

PHARMACOKINETICS:

Upon dose-normalization to 75 mg, an approximate dose-proportional increase was observed in serum concentration of tapentadol.

High intersubject variability (%CV) was observed for measured tapentadol, oxycodone, noroxycodone and oxymorphone serum concentrations for samples taken 1 hour after study drug intake on Day 1 (95.5% to 102% for tapentadol, 69.8% to 112.2% for oxycodone, noroxycodone, and oxymorphone). This high intersubject variability may be accounted for by the study design whereby subjects were permitted to take their second dose as soon as 1 hour after the first dose on Day 1. The intersubject variability for measured tapentadol and oxycodone serum concentrations for all other sampling times ranged from 40.5% to 53.6% and 41.4% to 53.3%, respectively, and for tapentadol, was similar in all dose groups. The observed variabilities were consistent with previous pharmacokinetic analyses of tapentadol and oxycodone (KF5503/22).

Based on calculations of accumulation ratios, it was concluded that the steady state of tapentadol was achieved in this study.

The serum concentration ratios of oxycodone metabolites to oxycodone (i.e., metabolite to parent ratio) for noroxycodone and oxymorphone were in the expected range, and the 2 oxycodone metabolites accumulated approximately in line with expectations after multiple dose administration.

EFFICACY RESULTS:

Primary efficacy variable: For $SPID_{48}$, all tapentadol IR treatment groups showed a statistically significant (p-values adjusted for multiple comparisons according to the Hochberg procedure and all <0.001) improvement in pain compared with placebo using the LOCF imputation method. There was a numerical trend of increasing efficacy with increasing tapentadol IR dose (mean $SPID_{48}$: 119.1, 139.1, and 167.2 in the tapentadol IR 50 mg, 75 mg, 100 mg groups, respectively). Oxycodone HCl IR 15 mg (mean $SPID_{48}$: 172.3) also showed a statistically

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significant (nominal p-value <0.001) difference from placebo (mean $SPID_{48}$: 24.5), validating the study assay sensitivity. Sensitivity analyses using BOCF and WOCF imputations also indicated statistically significant improvement for all active treatment groups versus placebo (all nominal p-values <0.001).

Secondary efficacy variables: The results for secondary efficacy variables supported the primary variable results. For time to first rescue medication use, there was a statistically significant difference in the distributions (all p-values adjusted for multiple comparisons according to the Hochberg procedure and <0.001), with longer times to rescue for tapentadol versus placebo and increasing time to rescue with increasing doses of tapentadol.

For distribution of responder rates based on pain intensity at 48 hours, a statistically significant difference was observed between each of the tapentadol IR groups and placebo (all nominal p-values <0.001). The proportions of subjects who showed at least a 30% improvement in pain intensity at 48 hours increased with increasing tapentadol IR dose: 40% with placebo, 65%, 68% and 79% of subjects with tapentadol IR 50 mg, 75 mg and 100 mg, respectively, and 78% with oxycodone HCl IR 15 mg (all nominal p-values <0.001).

For secondary pain scale variables that were statistically tested (SPID, TOTPAR, and SPRID), all tapentadol IR treatment groups showed statistically significant improvements (all nominal p-values <0.001) compared with the placebo group at all time points (12, 24, 48, and 72 hours). For variables not statistically tested (PID, PAR, PRID), numerical improvement of pain was observed with tapentadol IR compared with placebo.

For the time of onset of confirmed perceptible pain relief (recognized as an indicator of first onset of analgesia), the median time was 46, 32, 37, and 31 minutes for tapentadol IR 50 mg, 75 mg, 100 mg and oxycodone HCl IR 15 mg, respectively. The median time was 100 minutes for placebo-treated subjects.

For PGIC, all treatment groups showed a statistically significant difference in the distributions compared to placebo (all nominal p-values <0.001 in favor of the tapentadol IR).

For comparisons of tapentadol IR 75 mg to oxycodone HCl IR 15 mg, the composite incidence of nausea or vomiting showed a statistically significant advantage compared with oxycodone HCl IR 15 mg. However, the non-inferiority of tapentadol IR 75 mg to oxycodone HCl IR 15 mg based on $SPID_{48}$ could not be established.

The composite incidence of nausea or vomiting showed a statistically significant advantage of tapentadol IR 100 mg compared with oxycodone HCl IR 15 mg (post-hoc analysis). Tapentadol IR 100 mg was shown to be non-inferior to oxycodone HCl IR 15 mg based on $SPID_{48}$ (post-hoc analysis).

SAFETY RESULTS:

The overall percentage of subjects with treatment-emergent adverse events (TEAEs) in the double-blind period was higher than placebo for all active treatment groups. The the percentage of subjects in the oxycodone HCl IR 15 mg group (87%) was similar to that for the tapentadol IR 100 mg group (85%) and higher than those in the tapentadol IR 75 mg (75%) and 50 mg (70%) groups. During the double-blind period, the most common TEAEs included nausea, vomiting, constipation, dizziness, somnolence, headaches, and pruritus/pruritis generalised. Comparing subjects taking the highest tapentadol IR dose (100 mg) and those taking oxycodone HCl IR 15 mg, the incidence was lower with tapentadol IR 100 mg for nausea, vomiting, and constipation; was similar for dizziness; and was higher for somnolence. During the open-label period, TEAEs experienced by at least 5% of subjects included nausea, vomiting, headache, dizziness, and somnolence. Constipation was reported by 1% of subjects in the open-label period.

No subject died during the study or within 30 days of his/her last treatments. Four subjects (all during the double-blind period) had serious adverse events: 2 subjects in the placebo group had supraventricular tachycardia and transient ischemic attack, respectively; 1 subject in the tapentadol IR 50 mg group had a small bowel obstruction, and 1 subject in the tapentadol IR 75 mg group had pneumonia, viral myocarditis, and congestive heart failure. Treatment administered for over 9 days was well-tolerated.

Across the treatment groups, there was a low percentage of subjects with TEAEs associated with discontinuation during the double-blind period: 1% with placebo, 3% with tapentadol IR 50 mg, 5% with tapentadol IR 75 mg, 0% with tapentadol IR 100 mg and 2% with oxycodone HCl IR 15 mg. There was no treatment-related pattern in the TEAEs that led to treatment discontinuation.There were no TEAEs associated with discontinuation during the open-label period.

For the double-blind and open-label periods examination of mean values over time did not reveal clear or consistent patterns for urinalysis, vital signs or ECG. For laboratory tests, elevations in mean values during the study for alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) could be attributed to some outlying values, some of which were also documented as TEAEs. Examination of individual abnormal values for vital signs revealed single occurrences and TEAEs in the context of blood pressure and oxygen saturation decrease. In summary, the incidence of such single occurrences of variations was low and there was no apparent dose-related association of mean changes with tapentadol IR administration.

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PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

No pharmacokinetic/pharmacodynamic analysis was performed for this study.

PHARMACOGENOMICS:

As part of an exploratory analysis, the CYP2D6, CYP3A4, and CYP3A5 genes were genotyped. Based on the results, a predicted phenotype was assigned.

Exploratory genetic association analyses between genotypes in the CYP2D6, CYP3A4 and CYP3A5 genes and relevant clinical endpoints when performed will be reported separately.

CONCLUSION:

Tapentadol IR, in a fixed-dose regimen (50 mg, 75 mg, or 100 mg) administered every 4 to 6 hours, including an early second dose option on the first day, was effective in the treatment of moderate to severe acute pain during a 72-hour period following a bunionectomy when compared with placebo. A numerical trend of dose-response was observed for efficacy with all doses tested. Over a 12-day period (3 days for the double-blind period and 9 days for the open-label period), tapentadol IR was well tolerated with a safety profile similar to that of other centrally acting analgesics. Compared with the oxycodone HCl IR 15 mg group, the adverse event profile of tapentadol IR 100 mg appeared to have a higher incidence of somnolence, but all doses of tapentadol IR had a better gastrointestinal tolerability.

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