# SYNOPSIS

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| Name of Sponsor/Company | Grünenthal GmbH/Johnson & Johnson Pharmaceutical Research & Development, L.L.C. |
| Name of Finished Product | To be determined |
| Name of Active Ingredient(s) | Tapentadol Hydrochloride (also known as CG5503 and R331333) |

**Protocol No.:** R331333-PAI-1059; (HP5503/82)

**Title of Study:** A Single-Dose, Open-Label, Randomized, 2-Way Crossover Pivotal Study to Assess Bioequivalence of a New Tapentadol Extended-Release (TRF) 50-mg Tablet With Respect to a Tapentadol Extended-Release (PR2) 50-mg Tablet Under Fasted Conditions in Healthy Subjects

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**Publication (Reference):** None

**Study Period:** 30 July 2010 to 25 August 2010, Database lock: 3 September 2010.

**Phase of Development:** Phase 1

**Objectives:** The primary objective of the study was to evaluate the bioequivalence of the to-be-marketed tapentadol tamper-resistant formulation (TRF) 50-mg tablet produced at the commercial manufacturing site at Gurabo, Puerto Rico, US, to the current tapentadol prolonged-release (PR2) 50-mg tablet manufactured in Springhouse, PA, US used in pivotal Phase 3 efficacy studies in healthy subjects under fasted conditions. In addition, the safety and tolerability of tapentadol TRF and PR2 50-mg tablets were assessed in healthy subjects.

**Methods:** This was a single-dose, open-label, randomized, 2-way crossover study to establish the bioequivalence, safety, and tolerability of the to-be-marketed tapentadol TRF 50-mg tablet with the currently used tapentadol PR2 50 mg tablet in healthy men and women under fasted conditions. Sixty-four subjects, including men and women between 19 and 55 years of age, inclusive, were planned for this study.

The study consisted of 3 phases: a screening phase (within 21 days before the first study drug administration on Day 1 of Period 1), an open-label treatment phase consisting of 2 treatment periods, and an end-of-study (EOS) phase with assessments done upon completion of the 48-hour pharmacokinetic (PK) sampling on Day 3 of Period 2 or upon withdrawal. Study drug administration was separated by a washout period of at least 7 days and no more than 14 days. The approximate length of the study per subject was up to 5.5 weeks, including screening.

Eligible subjects were randomly assigned to 1 of 2 possible treatment sequences and received both of the following treatments, 1 in each period:

Treatment A: single oral dose of tapentadol TRF 50-mg tablet taken with 240 mL of noncarbonated water under fasted conditions

Treatment B: single oral dose of tapentadol PR2 50-mg tablet taken with 240 mL of noncarbonated water under fasted conditions

In each treatment period, subjects entered the study center on Day -1 at least 10 hours before study drug administration and remained there until completion of the 48-hour PK sample collection on Day 3 (Period 1), if the investigator considered that the subject was ready for discharge. On Day 1 of each period, a single dose of the appropriate study drug was administered to each subject between 7:00 and 10:00 AM

with 240 mL of noncarbonated water, followed by sequential collection of blood samples over 48 hours for measurement of serum concentrations of tapentadol. Subjects were to remain in an upright position from the time of study drug administration until 4 hours after study drug administration.

Before study drug administration in each treatment period, subjects were fasted for at least 10 hours. Subjects refrained from food until 4 hours after study drug administration. Subjects received standardized meals given at the same time in each treatment period. Subjects had a standard diet. Water was allowed ad libitum, except for 2 hours before and after study drug administration, when water was prohibited, except for study drug intake.

A subject was considered to have completed the study if the subject did not experience vomiting during the first 6 hours after the administration of study drug, completed all assessments as planned, did not meet withdrawal criteria, and completed all EOS procedures, including the 48-hour PK blood sample collections for both treatment periods.

**Number of Subjects (planned and analyzed):** Planned: Sixty-four healthy subjects including men and women were to be enrolled in the study to ensure at least 52 subjects complete all required assessments. Subjects were replaced if more than 12 subjects discontinued from the study before completion. Analyzed: Sixty-four subjects (32 men and 32 women) were enrolled in the study.

**Diagnosis and Main Criteria for Inclusion:** Healthy men and women between 19 and 55 years of age, inclusive; body mass index between 20 and 28 kg/m², inclusive, and a body weight of not less than 50 kg.

**Test Product, Dose and Mode of Administration, Batch No.:** Single oral dose of tapentadol TRF 50-mg tablet (Batch No: 9EG9279-X was administered with 240 mL of noncarbonated water under fasted conditions (Treatment A).

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Single oral dose of tapentadol PR2 50-mg tablet (Batch No: PD3137) was administered with 240 mL of noncarbonated water under fasted conditions (Treatment B).

**Duration of Treatment**: Single doses of tapentadol as per assigned treatment sequence were administered in each treatment period separated by washout period of at least 7 and no more than 14 days. The length of the study including the screening and washout periods was approximately 5.5 weeks per subject.

**Criteria for Evaluation:**

Pharmacokinetics: Blood samples (4 mL each to obtain approximately 2 mL of serum) were collected for a determination of tapentadol serum concentrations for a 48-hour period after both treatments. The following key PK parameters were calculated: observed maximum serum concentration ($C_{max}$), time to reach the observed maximum serum concentration ($t_{max}$), area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration $C_{last}$ ($AUC_{last}$), area under the serum concentration-time curve from time zero to infinite time, calculated as the sum of $AUC_{last}$ and $C_{last}/\lambda z$ ($AUC_{\infty}$), percentage of $AUC_{\infty}$ obtained by extrapolation (%$AUC_{\infty}$, ex), first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve ($\lambda z$), elimination half-life associated with the terminal slope ($\lambda z$) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda z$ ($t_{1/2,\lambda}$), time to last quantifiable serum concentration ($t_{last}$), and relative bioavailability of tapentadol calculated as the AUC and $C_{max}$ ratios (%) of Treatment A/Treatment B (ie, treatment effect) ($F_{rel}$).

Safety: Safety and tolerability were evaluated throughout the study based on adverse event monitoring, clinical laboratory tests (hematology and chemistry), urine drug screen, alcohol urine test, pregnancy test, and serology (for screening and eligibility), 12-lead electrocardiogram (ECG), vital sign measurements (respiratory rate, blood pressure, pulse rate, and body temperature), and physical examination.

The total amount of blood to be drawn for clinical laboratory tests and PK evaluations was approximately 155 mL.

**Statistical Methods:**

At least 52 subjects were to complete all study procedures, including the 48-hour PK blood sample collections, and the EOS evaluations.

Sample Size Determination: The intrasubject coefficient from 3 previous bioavailability studies and 2 previous bioequivalence studies comparing tapentadol PR2 with TRF tablets were estimated ranging from 4% to 20%. Using an estimated intrasubject coefficient of variation of 20% for AUCs and $C_{max}$ and a 5% level of significance, a sample size of 52 subjects who complete the study would be sufficient to conclude bioequivalence between the tapentadol TRF 50-mg tablets and tapentadol PR2 50-mg tablets with 90% power, when the 2 treatment means differ by 10%. Sixty-four subjects were to be enrolled to allow for a dropout/withdrawal rate of 18%. Subjects were replaced if more than 12 subjects withdrew from the study before completion.

Pharmacokinetics: For each treatment, descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, ratio of mean (PK parameters only), median, minimum, and maximum were calculated for tapentadol serum concentrations at each sampling time and for all PK parameters of tapentadol. The descriptive statistical analysis of PK parameters was performed twice (Analysis 1 and Analysis 2) as described below.

The descriptive statistics of Analysis 1 included 55 subjects for $AUC_\infty$ and $t_{1/2}$ following administration of the TRF formulation and 39 subjects for these PK parameters following administration of the PR2 formulation. Twenty subjects were excluded from the descriptive statistical analysis (Analysis 1) of PK parameters $t_{1/2}$ and $AUC_\infty$ due to the linear regression $R^2$ adjusted value being less than 0.900 during estimation of the terminal phase ($\lambda_z$) of the concentration-time profile, 3 subjects were excluded due to an inadequate (<3) number of samples included in $\lambda_z$ calculations, and 3 subjects were excluded in whom both occurred. Sixty-two subjects were included in the descriptive statistics of $t_{max}$, $C_{max}$, and $AUC_{last}$ for both formulations during Analysis 1.

The descriptive statistics of Analysis 2 included 62 subjects for $AUC_\infty$ and $t_{1/2}$ following administration of the TRF formulation and 61 subjects for these PK parameters following administration of the PR2 formulation. The %AUC extrapolated exceeded 20% for 1 subject after the administration of the PR2 formulation. Sixty-two subjects were included in the descriptive statistics of $t_{max}$, $C_{max}$, and $AUC_{last}$ for both formulations during Analysis 2.

The primary parameters of interest for the statistical analysis were $AUC_{last}$, $AUC_\infty$, and $C_{max}$ of tapentadol. The analysis was performed on log-transformed estimated PK parameters A mixed-effect model that included treatment, period, and treatment sequence as fixed effects, and subject as random effect was used to estimate the least squares means and intrasubject variance. Using these estimated least squares means and intrasubject variance, the point estimate and 90% confidence intervals (CI) for the difference in means on a log scale between Treatment A and Treatment B were constructed. The limits of the CI were retransformed using antilogarithms to obtain 90% CI for the ratios of the mean values for AUC and $C_{max}$ of the test to reference formulation (tapentadol TRF 50 mg/tapentadol PR2 50 mg). Tapentadol TRF 50 mg and tapentadol PR2 50 mg were considered bioequivalent if the 90% CI for the ratio of the means (TRF/PR2) fell within 80% to 125%.

The inferential statistical analysis of $C_{max}$ and $AUC_{last}$ included 60 subjects who completed the study. Subjects were excluded from the analysis of $AUC_\infty$ if the reasons summarized above were applicable in either one of the treatment periods. For the reasons summarized above, the statistical analysis of $AUC_\infty$ was conducted twice as follows. Analysis 1 included 34 subjects and Analysis 2 included 59 subjects. The results of Analyses 1 and 2 produced similar conclusions with respect to the assessment of bioequivalence based on $AUC_\infty$.

Safety: All subjects who entered the study and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline for all laboratory evaluations and 12-lead ECG measurements were defined as the last evaluation done before the first study drug administration and for vital signs as the last evaluation done before the study drug administration of each period. Safety was evaluated by

examining the incidence and type of adverse events, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs and vital signs measurements from the screening phase through study completion, including the washout interval.

Pharmacodynamic Analysis: There was no pharmacodynamic analysis was planned in this study.

Pharmacokinetic/Pharmacodynamic Analysis: There was no pharmacokinetic/pharmacodynamic analysis planned in this study.

Pharmacogenomics: There was no pharmacogenomic analysis planned in this study.

**RESULTS:**

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: Sixty-four subjects (32 men and 32 women) were randomized in this study and assigned to 1 of 2 treatment sequences. Seventy-eight percent of the subjects were White, 11% were Black or of African Descent, 8% were Hispanic or Latino, 2% were Asian, and 2% were American Indian or Alaskan Native. There was a higher percentage of White subjects in the PR2/TRF treatment sequence group compared to the TRF/PR2 treatment sequence group (81% and 75%, respectively) and the percentage Black or of African Descent subjects in the TRF/PR2 and PR2/TRF treatment sequence groups was similar (13% and 9%, respectively). There were no clinically relevant differences between median values of age, weight, height, or body mass index among the subjects in each treatment sequence.

PHARMACOKINETIC RESULTS:

Maximum serum concentrations of tapentadol were reached at a median $t_{max}$ of 5 hours for both formulations with comparable minimum to maximum ranges. However, the mean $C_{max}$ values were numerically higher following treatment with the TRF formulation as compared with the PR2 formulation ($C_{max}$ 16.9 and 12.8 ng/mL, respectively). Tapentadol exposure was similar between the 2 treatments based on $AUC_{last}$ (236 and 215 ng·h/mL, respectively) and $AUC_{\infty}$ (245 and 229 ng·h/mL, respectively) from Analysis 1 and $AUC_{\infty}$ (242 and 224 ng·h/mL, respectively) from Analysis 2. On average, the mean apparent $t_{1/2}$ was approximately 2 hours shorter for the TRF 50 mg formulation (approximately 6 hours) compared with the PR2 50 mg formulation (approximately 8 hours).

The results of the inferential statistical analyses are summarized in the table below. The point estimate of the ratio (TRF tablet versus PR2 tablet) of means for $C_{max}$ was 129.26%. The lower and upper boundaries of the corresponding 90% CI were 123.46% and 135.34%, respectively, which exceeds the upper limit of the 80% to 125% range used for demonstrating bioequivalence. The estimated ratios of mean $AUC_{last}$ and $AUC_{\infty}$ were similar based on Analysis 1 (110.04% and 107.97%, respectively) and for $AUC_{\infty}$ from Analysis 2 (108.91%). All corresponding 90% CIs for $AUC_{last}$ and $AUC_{\infty}$ were within the 80% to 125% range of bioequivalence.

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study R331333-PAI-1059; HP5503/82: Pharmacokinetic Data Analysis Set)

| PK Parameter | N | Tapentadol TRF 50 mg LSM | Tapentadol PR2 50 mg LSM | Ratio TRF/PR2 | 90% CI | %CV |
|---|---|---|---|---|---|---|
| $C_{max}$, ng/mL | 60 | 16.04 | 12.41 | 129.26 | 123.46 - 135.34 | 15.1 |
| $AUC_{last}$, ng·h/mL | 60 | 224.72 | 204.22 | 110.04 | 105.66 - 114.60 | 13.4 |
| $AUC_{\infty}$, ng·h/mL[a] | 34 | 246.07 | 227.91 | 107.97 | 101.26 - 115.13 | 15.0 |
| $AUC_{\infty}$, ng·h/mL[b] | 59 | 233.41 | 214.32 | 108.91 | 104.42 – 113.58 | 13.7 |

[a] From Analysis 1
[b] From Analysis 2
CI = confidence interval, %CV = % coefficient of variation, LSM = least squares mean
N = number of subjects included in the inferential statistical analysis
TRF = tamper-resistant formulation (to-be-marketed formulation)
PR2 = prolonged release formulation 2 (used in the Phase 3 studies)

SAFETY RESULTS: Overall, the percentage of subjects with treatment-emergent adverse events was higher for tapentadol TRF 50 mg compared with tapentadol PR2 50 mg. The most commonly reported treatment-emergent adverse event (≥10% for any treatment) was headache (11% for tapentadol TRF 50 mg and 10% for tapentadol PR2 50 mg). All the adverse events reported in the study were mild in severity. Most of the treatment-emergent adverse events resolved during the study. Five subjects received paracetamol (acetaminophen) as a concomitant medication for the treatment of adverse events. There were no deaths, serious adverse events, or discontinuations due to an adverse event during the study. There were no clinically relevant changes in ECG findings noted during the study.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSIONS:

The TRF and PR2 tablet formulations of tapentadol ER 50 mg were bioequivalent based on the estimates of serum $AUC_{last}$ and $AUC_{\infty}$. Bioequivalence was not demonstrated based on serum $C_{max}$.

The overall safety profile was similar for the tapentadol TRF and PR2 50-mg formulations and both formulations were well tolerated in healthy subjects.

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