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 HCl (also known as CG5503 and R331333)

Protocol No.: R331333–PAI–1036 (HP5503/38)

Title of Study: An Open-Label, Sequential Treatment Study to Assess the Single- and Multiple-Dose Pharmacokinetics of a New Tapentadol Extended-Release 250-mg Formulation in Healthy Subjects.

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Publication (Reference): None

Study Period: 19 September 2008 to 13 October 2008, Database lock: 20 November 2008

Phase of Development: Phase 1

Objectives: Primary: To assess the single-dose pharmacokinetics (PK) of tapentadol and compare with the multiple-dose PK of tapentadol following multiple administrations of tamper resistant extended-release formulation (tapentadol TRF) 250-mg tablets in healthy subjects.

Secondary: To describe for tapentadol-O-glucuronide, the PK behavior following single and multiple administrations of tapentadol TRF 250-mg tablets in healthy subjects.

In addition the safety and tolerability was also assessed.

Methods: This was a single-center, single- and multiple-dose open-label, and sequential treatment study to evaluate the multiple-dose PK of the tapentadol TRF 250-mg tablet, in comparison to the single-dose PK of tapentadol TRF 250-mg tablet.

The study consisted of 3 phases: a screening phase (within 2 to 21 days before the first administration of the study drug); an open-label treatment phase in which subjects received a single-dose of study drug followed by multiple-doses of study drug (total of 5 doses twice daily [b.i.d.]) and had PK, safety, and tolerability assessments, and an end-of-study (EOS) phase with evaluations upon completion of the last PK sampling on Day 8 or at early withdrawal.

The single-dose and the first dose of the multiple-dose treatment were separated by an additional washout period of 24 hours after the last PK blood sample on Day 3. The duration of participation in the study for an individual subject was 29 days (including screening).

Subjects sequentially received a single oral dose of tapentadol 250-mg TRF tablet administered to each subject on Day 1 of the study between 8:00 and 10:00 a.m. after a standardized breakfast and multiple doses of tapentadol 250-mg TRF tablet each administered every 12 hours on Days 4, 5 and 6 (total of 5 doses).

Subjects entered the study center on Day -1 at least 10 hours before study drug administration and remained there until after collection of the final PK sample on Day 8 if the investigator considered that the subject was ready for discharge.

A pharmacogenomic blood sample was collected from subjects who consented separately to the pharmacogenomic component of the study and their participation in pharmacogenomic research was optional. 10-mL blood sample was collected from subjects who consented to participate in the pharmacogenomics component of the study.

Number of Subjects (planned and analyzed): Eighteen subjects (6 males and 12 females) were planned and enrolled in the study to ensure that 10 subjects completed the study. Replacement by a subject of the same sex was done if less than 10 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were healthy males and non-pregnant and non-lactating females, between 18 and 55 years of age, 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.: Tapentadol TRF tablets 250-mg. (08G09-F033; expiration date Sep 2009) were administered as single oral dose on Day 1 and multiple oral dose on Day 4, 5, and 6 (b.i.d. for 5 doses total) with 240 mL of noncarbonated water.

Duration of Treatment: Subjects received tapentadol TRF tablets 250-mg as single dose on Day 1 and b.i.d. for 5 doses on Days 4, 5, and 6. The maximum duration of participation in the study for an individual subject was 29 days including screening.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for determination of tapentadol and tapentadol-O-glucuronide serum concentrations were collected on Day 1 (predose), Day 2, and 3 (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose), Day 4 and 5 (predose, 4, 12, 16, 24, 28, 36, and 40 hours postdose), Day 6 and 7 (predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours postdose), and Day 8 (48 hours postdose). The following key PK parameters were calculated: C_{max}, t_{max}, t_{last}, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, $t_{1/2,\lambda}$, λ_z, $C_{max,ss}$, C_{trough}, $t_{max,ss}$, $AUC_{\tau,}$ $C_{avg,ss}$, FI, and ACC ratio.

Safety: The safety evaluations consisted of adverse events, physical examination, vital signs (temperature, pulse rate [supine], respiratory rate, blood pressure [BP][supine]), 12-lead electrocardiogram (ECG), clinical laboratory values, serology values, urine drug screening, serum and urine beta-human chorionic gonadotropin (beta-HCG) values, and alcohol breath test.

Pharmacogenomics: A pharmacogenomic blood sample (10 mL) was collected at Day 1 predose to allow for pharmacogenomic research, as necessary.

The total amount of blood to be drawn for clinical laboratory tests, PK evaluations, and optional pharmacogenomic research was approximately 244 mL.

Statistical Methods:

Sample Size Determination: The number of subjects selected for this study was not based on formal statistical consideration. A sample size of 10 subjects completing the study was expected to be sufficient to characterize the PK profile for the single- and multiple-dose PK of tapentadol following 5 doses at a b.i.d. administration scheme of tapentadol TRF 250-mg. Assuming an intra-subject coefficient of variation of 25% for AUC and C_{max} after single and multiple-dose administration of tapentadol 250-mg TRF, a sample size of 10 subjects was sufficient for the point estimate of the ratio of mean PK parameters between single and multiple-dose of tapentadol 250-mg TRF to fall within 78% and 128% of the true value with 90% confidence. An unequal number of males and females were enrolled in this study. This was based on the notable difference in dropout numbers between males and females in previous studies, mainly due to vomiting. Using the estimated dropout rates for males and females of 15% and 58%, respectively, 18 healthy subjects (6 males and 12 females) were enrolled in the study. Subjects were replaced if less than 10 subjects completed the study.

Pharmacokinetics: Descriptive statistics for PK parameters was presented for tapentadol TRF 250-mg tablet after a single dose and after multiple doses. Data was listed for all subjects with available serum concentrations and all concentrations below the limit of quantification or missing data were labeled as such in the concentration data listings. Concentrations below the limit of quantification were treated as zero in the summary statistics and for the calculation of PK parameters. Factors likely to influence the serum concentrations (e.g., vomiting, diarrhea, comedication, fever, high predose concentration) were checked. All subjects and samples excluded from the analysis were clearly documented in the study report.

For each treatment, descriptive statistics, including arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum were calculated for tapentadol and tapentadol-O-glucuronide serum concentrations at each sampling time and for all PK parameters of tapentadol and tapentadol-O-glucuronide.

Graphical representations of the results included, but were not limited to, the log-linear and linear-linear serum concentration-time profiles for each individual, for arithmetic mean values, and for the median values, as well as log-linear and linear-linear overlay plots of the individual serum concentration-time profiles graphs for tapentadol and tapentadol-O-glucuronide.

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

RESULTS:

DEMOGRAPHIC CHARACTERISTICS AND BASELINE CHARACTERISTICS: Majority subjects were white (89%) and the overall median age was 29.5 years (range of 19 to 53 years). The median BMI of subjects was 23 kg/m^2 (range of 21 to 28 kg/m^2).

PHARMACOKINETIC RESULTS: For the evaluation of the steady state conditions, the mean concentrations of tapentadol were assessed at 0, 4, 12, 16, 24, 28, 36 and 40 hours and were below the quantification limits, 65.4, 50.3, 80.7, 68.9, 109, 70.6, and 107 ng/mL, respectively. It can be concluded that steady state of tapentadol was reached in this study within the predicted time frame of about 20 to 25 hours after start of dosing.

Pharmacokinetic data from all 18 subjects (7 males and 11 females) in the study were analyzed. Some individual PK parameters or serum concentrations of tapentadol and tapentadol-O-glucuronide were excluded from the descriptive statistics either due to vomiting, no or incorrect time registration or early withdrawal of the subject from the study. A summary of the mean serum PK parameters for tapentadol as calculated from the concentration-time profile on Day 1 and Day 6 are presented in the table below.

Summary of Descriptive Statistics of the Pharmacokinetic Parameters of Tapentadol (Study R331333-PAI-1036 (HP5503/38): Pharmacokinetic Analysis Set)

Pharmacokinetic Parameters (units)	n	Tapentadol TRF 250 mg Mean ± SD	%CV
Day 1			
C_{max}, ng/mL	15	88.0 ± 27.8	31.6
t_{max}, h	15	5.00 (2.00-12.00)	
AUC_{0-12h}	15	651 ± 202	31.1
AUC_{∞}, h.ng/mL	15	1070 ± 303	28.3
$t_{1/2}$, h	15	4.4 ± 0.8	17.9
Day 6			
$C_{max,ss}$, ng/mL	17	132 ± 35.1	26.7
$t_{max,ss}$, h	17	5.00 (2.00-10.02)	
AUC_{τ}, h.ng/mL	16	1144 ± 339	29.7
$C_{avg,ss}$, ng/mL	16	95.2 ± 28.1	29.5
$t_{1/2}$, h	16	5.2 ± 1.0	18.8
FI, %	16	65.3 ± 27.1	41.4
Acc. Ratio (C_{max})	17	1.60 ±0.605	37.7
Acc. Ratio (AUC)	14	1.86 ± 0.552	29.7

t_{max}: median (min-max)
TRF=tamper resistant prolonged-release formulation; SD=standard deviation; CV=coefficient of variation

Upon single dose treatment, the average maximum serum concentration for tapentadol was 88.0 ng/mL and overall exposure (AUC_{∞}) was 1070 ng/mL. During the multiple dose phase, the calculated mean tapentadol, $C_{max,ss}$, was 132 ng/mL, $C_{avg,ss}$ 95.2 ng/mL and AUC_{τ} was 1144 ng/mL after administration of the fifth dose of tapentadol TRF 250 mg. The mean fluctuation index was less than 1 for indicating low fluctuation in serum concentration over the dosing period after steady state was achieved. The mean accumulation ratio (C_{max}) of 1.60 was consistent with previously reported values using the approximate C_{max} values after single-and multiple-dose administration of the immediate release formation.

Mean peak tapentadol serum concentrations were achieved 5 hours (median) postdose for Day 1 as well as Day 6 and terminal half-life averaged 4.4 and 5.2 hours, respectively for single and multiple dosing. These were consistent with the results from previous studies with the TRF formulation.

PHARMACODYNAMIC RESULTS: No pharmacodynamic evaluations were performed in this study.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS: No PK/pharmacodynamic evaluations were performed in this study.

PHARMACOGENOMIC RESULTS: DNA collection was included in this study. No genotyping analysis was completed.

SAFETY RESULTS: There were no deaths, serious adverse events, or any discontinuations due to adverse events during this study. Overall, the percentage of subjects with TEAEs after single dose treatment was comparable to that after multiple-dose treatment with tapentadol TRF 250 mg. The most commonly reported TEAEs were somnolence (100%), dizziness (67%), fatigue (50%), pruritis (50 %), headache (44%), and nausea (33%). All the adverse events reported in both treatment groups, were either mild or moderate in severity and majority resolved spontaneously at the end of study/follow up period. Most

adverse events were considered by the investigator to be related to the study drug. Few clinically relevant changes were observed in laboratory values, vital signs, and ECG values, but none of them were reported as adverse event by the investigator. Tapentadol TRF formulation was safe and well tolerated in single-dose and multiple-dose administrations.

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

CONCLUSION: The single dose PK parameters for tapentadol and tapentadol-O-glucuronide were consistent with previous studies of the TRF formulation in healthy subjects. The multiple dose PK parameters for tapentadol and tapentadol-O-glucuronide were predictable based on the single dose kinetics.

Tapentadol TRF formulation was well tolerated in single dose and multiple dose administrations.

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