Trial code	HP5503-93
Title of trial	A randomized, single-site, open-label, 2-way crossover, single-dose Phase I clinical trial to assess the bioequivalence of 2 tablets of a tapentadol 25 mg prolonged-release tablet formulation and 1 tablet of a tapentadol 50 mg prolonged-release tablet formulation in healthy male subjects under fed conditions.
Trial design	Randomized, single-site, open-label, 2-way crossover, single-dose Phase I clinical trial.
Development phase	Phase I
EudraCT number	2017-003904-39
Universal Trial Number	U1111-1202-5348
Investigational medicinal product (IMP)	Tapentadol prolonged release (PR)
Indication	Not applicable
Principal investigator	[redacted], MD, MSc, Research Physician C-EDS-NL; PRA Health Sciences
Trial site	The Netherlands (1 site)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted] MD Head Clinical Science
	Contact number: +49 (0) 241-569-0
Trial period	First subject in: 07 May 2018
	Last subject out: 26 Jul 2018

Objectives

Primary objective

To demonstrate the bioequivalence of 2 tablets of a tapentadol PR 25 mg tablet formulation and 1 tablet of a tapentadol PR 50 mg tablet formulation after single oral administration under fed conditions.

Secondary objectives

To assess further pharmacokinetic parameters.

To assess the safety and tolerability of both treatments.

Investigational medicinal product

Test formulation

Tapentadol hydrochloride formulation, a PR tablet containing 25 mg of tapentadol.

Batch number: 313I, expiration date: Sep 2020.

Reference formulation

Tapentadol hydrochloride PR2small formulation, a PR tablet containing 50 mg of tapentadol.

Batch number: 981I, expiration date: Mar 2020.

Trial treatments

A single dose of 2 tablets of the Test formulation (i.e., 2 x 25 mg) or 1 tablet of the Reference formulation (50 mg) were administered with 240 mL of non-carbonated water under fed conditions (after intake of a standard high-fat and high-calorie breakfast) on Day 1 of Treatment Period 1 and Treatment Period 2 using an open-label, randomized, 2-way crossover design.

Trial population

Written informed consent to participate was required from all subjects.

Subjects had to be male, White, aged 18 years to 55 years, inclusive, be in good health as determined by their medical history and physical examination, and not show any clinically significant deviations from reference ranges as determined by 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature), and safety laboratory parameters (hematology, clinical chemistry, clotting, and urinalysis). They had to be able to eat and finish the high-fat and high-calorie breakfast.

Summary of the trial procedures and assessments

The trial comprised of an Enrollment Visit (2 days to 28 days before the first administration of the IMP), 2 treatment periods (of 4 days duration beginning from about 18 hours before administration of the IMP and ending at about 48 hours after administration of the IMP), a washout period separating the 2 treatment periods (7 days to 14 days between administrations), and a Final Examination (2 days to 7 days following discharge from the last treatment period).

Each subject was expected to be in the trial for up to 8 weeks.

At the Enrollment Visit, demographic data (including height, body weight, and calculation of body mass index), medical history, findings from a physical examination and 12-lead ECG, vital signs, and results of an alcohol urine test and drugs of abuse test were recorded. Blood was sent for virus serology and safety laboratory parameter (including thyroid stimulating hormone) analysis. Urinalysis was also performed. The tests were repeated as applicable during the trial.

Blood for the evaluation of serum concentrations of tapentadol was taken before IMP dosing, and at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours after IMP dosing.

Trial performance

There was 1 protocol amendment. There was no premature trial termination or suspension (clinical hold) of the trial.

Summary of the statistical methods

Sample size rationale

Based on the estimates of former bioavailability/bioequivalence trials HP5503-76 (PR2 versus PR, dose 50 mg) and HP5503-52 (PR2 formulations, dose 150 mg), which were conducted under fed conditions (high-fat and high-calorie meal), the maximal intra-subject coefficient of variation (CV%) for C_{max}, AUC_{0-t}, and AUC (AUC_{0-inf}) following treatment with 2 tapentadol PR formulations varied from 15% to 17%. Using an estimation of intra-subject CV equal to 18% and assuming the true ratio Test versus Reference of geometric means 1.10, a sample size of 36 subjects was sufficient for the 90% confidence interval of the average relative bioavailability of the Test with respect to Reference formulation to fall within 80% to 125% with 90% likelihood.

It was foreseen that 40 subjects would be allocated to treatment with the aim that at least 36 subjects completed the trial.

Subject populations

Enrolled Set:	Included all subjects who signed the informed consent form.
Allocated Set:	Included all subjects who were allocated to treatment. Analyses based on the Allocated Set were conducted according to the allocated treatment.
Safety Set:	Included all subjects with at least 1 IMP administration. Analyses based on the Safety Set were conducted on the actual treatment received.
Pharmacokinetic Set:	Included all subjects having both treatment periods evaluable with respect to the pharmacokinetic parameters and who had no key protocol deviations potentially affecting the evaluation of the main pharmacokinetic parameters. The Pharmacokinetic Set was the primary population for the statistical analysis of pharmacokinetic parameters. Subjects vomiting within 12 hours after IMP administration were to be withdrawn from the trial and excluded from the Pharmacokinetic Set. Subjects with a pre-dose concentration higher than 5% of the subsequent Cmax were also to be excluded from the Pharmacokinetic Set.
Extended Pharmacokinetic Set:	Included all subjects who provided samples from at least 1 treatment period and had no key protocol deviations potentially affecting the evaluation of the main pharmacokinetic parameters.

Pharmacokinetic analysis

For each treatment involving administration of tapentadol, descriptive statistics were calculated for tapentadol serum concentrations at each sampling time and for all pharmacokinetic parameters. The pharmacokinetic parameters were displayed by subject.

The primary parameters of interest for the statistical analysis were C_{max}, AUC_{0-t}, and AUC of tapentadol. The analysis was performed on log-transformed pharmacokinetic parameters. Analysis of variance models were fitted to the data with 1 of the pharmacokinetic parameters of interest as the dependent variable, the effects due to treatment sequence group, period, and treatment as fixed effects, and subjects nested within the sequence group as random effect. Testing for the treatment

sequence group effect was carried out by using the mean square due to the subjects nested within treatment sequence groups as the error term; testing for the treatment and period effect was carried out at a 5% level of significance using the residual error term. The estimated least square means and intra-subject variance from the above model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 formulations. The limits of the confidence intervals were retransformed using antilogarithms from 90% confidence intervals for the ratio of the mean for each of the pharmacokinetic parameters of tapentadol for the Test and Reference formulations.

Bioequivalence was concluded if the 90% confidence intervals for the ratio of mean C_{max}, AUC_{0-t}, and AUC values of the 2 formulations fell within the limits of 80% and 125%.

The analysis of the main parameters of interest was based on the Pharmacokinetic Set and Extended Pharmacokinetic Set.

Safety analysis

All safety and tolerability parameters (adverse events, vital signs, 12-lead ECG, and laboratory monitoring) were listed by subject and treatment group. All analyses were performed for the Safety Set by treatment.

All safety and tolerability parameters were analyzed descriptively. Summary statistics were provided for the differences to baseline (e.g., Final Examination versus Enrollment Visit, and post-dose versus pre-dose, if appropriate).

Summary of results

Subject disposition

Of the 96 subjects enrolled into the trial, a total of 40 were allocated to and were treated with IMP. Thirty-eight subjects (95.0%) completed the clinical trial. Two subjects (5.0%) discontinued the trial. Thirty-nine subjects (97.5%) were considered to be treatment completers (i.e., treated subjects who completed IMP administration according to the protocol).

Demographics

All subjects were healthy White male subjects aged 18 years to 50 years. Overall, the mean age of the subjects was 23.8 years, their body weight ranged between 63.0 kg and 105.1 kg with a mean of 78.67 kg, and their body mass index ranged between 20.0 kg/m^2 and 27.2 kg/m^2 with a mean of 23.51 kg/m^2.

Pharmacokinetics

The following table presents a summary of statistical analyses of C_{max}, AUC_{0-t}, and AUC of tapentadol for the Pharmacokinetic Set (38 subjects).

Parameter	CV [%]	Ratio of LS means: Tapentadol PR 2 x 25 mg / Tapentadol PR2small 50 mg	90% CI of ratio
C_{max} [ng/mL]	13.6	108.8	(103.3, 114.7)
AUC_{0-t} [h*ng/mL]	9.4	104.7	(100.9, 108.5)
AUC [h*ng/mL]	9.4	104.9	(101.1, 108.8)

CI = confidence interval; CV = coefficient of intra-subject variation; LS means = least square means

The 90% confidence intervals for the ratios of C_{max}, AUC_{0-t}, and AUC for the 2 tablets of the 25 mg tapentadol PR formulation (Test) compared to the 1 tablet of the 50 mg tapentadol PR2small formulation (Reference) fell within the 80% to 125% range used for assessing bioequivalence. Therefore, the bioequivalence (with regard to C_{max}, AUC_{0-t}, and AUC) of 2 tablets of the 25 mg tapentadol PR formulation and 1 tablet of the 50 mg tapentadol PR2small formulation under fed conditions after single oral administration was demonstrated.

Safety and tolerability results

The frequency of TEAEs was similar after both treatments: 29 TEAEs were reported in 19 of 40 subjects (47.5%) after 2 tablets of 25 mg tapentadol PR and 35 TEAEs were reported in 21 of 39 subjects (53.8%) after 1 tablet of 50 mg tapentadol PR2small.

The most frequently reported TEAEs after administration of 2 tablets of 25 mg tapentadol PR were nervous system disorders (headache, somnolence, and dizziness) with 15 TEAEs in 11 subjects (27.5%) followed by general disorders and administration site conditions (fatigue, catheter site related reaction, and catheter site pain) with 6 TEAEs in 6 subjects (15.0%).

The most frequently reported TEAEs after administration of 1 tablet of 50 mg tapentadol PR2small were nervous system disorders (headache, somnolence, and dizziness) with 16 TEAEs in 12 subjects (30.8%) followed by general disorders and administration site conditions (fatigue, catheter site related reaction, catheter site paraesthesia, and feeling hot) with 10 TEAEs in 10 subjects (25.6%).

All TEAEs were of mild intensity.

Approximately half of the TEAEs were judged as related to IMP by the investigator (48.3% after administration of 2 tablets of 25 mg tapentadol PR and 45.7% after administration of 1 tablet of 50 mg tapentadol PR2small).

There were no deaths, other serious adverse events, or adverse events leading to discontinuation.

No clinically relevant influence of either treatment on safety laboratory parameters, vital signs, physical status, or 12-lead ECG measurements was observed.

Conclusions

- Bioequivalence was demonstrated between 2 tablets of the tapentadol 25 mg PR formulation and 1 tablet of the tapentadol 50 mg PR2small formulation under fed conditions.
- Single dose administrations of 2 tablets of 25 mg tapentadol PR and 1 tablet of 50 mg tapentadol PR2small were well tolerated.
- The TEAEs reported were mostly expected, similar between the Test treatment and Reference treatment, and reflected the known safety profile of tapentadol or trial procedures.
- No new safety issues or adverse drug reactions were identified.