SYNOPSIS

Issue Date: 28 February 2012
Document No.: EDMS-ERI-10997384: 4.0

Name of Sponsor/Company	Janssen Research and Development*
Name of Finished Product	ULTRAM ER®
Name of Active Ingredient	Tramadol Hydrochloride

Protocol No.: TRAMAPPAI1003

Title of Study: A Single Dose Pharmacokinetic, Tolerability, and Safety Study of ULTRAM ER® at Two Dose Levels in Adolescents Twelve to Seventeen Years Old, Inclusive, With Pain.

Principal Investigator: Margaret Ann Springer, MD, Louisiana University Health Sciences Center, Shreveport Louisiana, USA

Publication (Reference): None

Study Period: 06 November 2007 to 22 September 2008

Phase of Development: 1

Objectives: The primary objective of this study was to compare the pharmacokinetics (PK) of single oral doses of ULTRAM extended release (ER) at 2 dose levels in adolescents between 12 and 17 years old, inclusive (up to 17 years 364 days) with pain due to injury or nonmalignant disease, and to compare with the PK from historical data in adults, with respect to the PK parameter area under the plasma concentration-time curve of racemic tramadol from time 0 to infinite time (AUC_∞).

The secondary objectives of this study were:

- To explore the PK of single oral doses of ULTRAM ER at 2 dose levels in adolescents between 12 and 17 years old, inclusive (up to 17 years 364 days) with pain due to injury or nonmalignant disease, with respect to other PK parameters (including area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration [AUC_{last}], maximum plasma concentration [C_{max}], time to reach the maximum plasma concentration [t_{max}], total clearance of drug after extravascular administration, [CL/F], apparent volume of distribution after extravascular administration [Vd/F], and elimination half-life [$t_{1/2}$] of racemic tramadol and the [+] and [-]-enantiomers of tramadol; AUC_∞, AUC_{last}, C_{max}, t_{max}, and apparent $t_{1/2}$ of racemic metabolites M1 and *N*,O-didesmethyl tramadol [M5] and the [+] and [-]-enantiomers of M1 and M5);
- To graphically explore the PK of single oral doses of ULTRAM ER at 2 dose levels in adolescents between 12 and 17 years old, inclusive (up to 17 years 364 days), with pain due to injury or nonmalignant disease versus the PK in adults;
- To evaluate the preliminary tolerability and safety of single oral doses of ULTRAM ER at 2 dose levels in adolescents between 12 and 17 years old, inclusive (up to 17 years 364 days) with pain, who may be receiving other concomitant pain medications, due to injury or nonmalignant disease.

Methods: This was a multicenter, open-label, 2-group, single dose study. Thirty-six subjects were planned to be enrolled; 6 subjects in Group 1 and 30 subjects in Group 2. Within each group, at least one-third of the subjects had to be females, one-third of subjects had to be males, one-third of subjects had to be below the age of 14 years (up to 13 years 364 days), and one-third of subjects had to be above the age of 16 years. Subjects were assigned to any one group only. Subjects in Group 1 received a dose of study drug that was closest to 2 mg/kg, based on the subject's body weight and adjusting the dose in 25 mg increments on Day 1. Following completion of all evaluations of Group 1, the PK data were to be evaluated to target a dose for Group 2 that would achieve a level of exposure similar to that seen with a single 200 mg ULTRAM ER dose in adults (AUC_∞=5,000 ng·hour/mL). Enrollment for Group 2 was to begin if the study drug was judged by the sponsor's study physician, investigators, and medical monitors to be safe and well-tolerated and if the PK of the drug was well-characterized. Subjects were to be

admitted to study center prior to dosing either on the evening of Day –1 or the morning of Day 1 and were to remain in the study center until after the 24 hour PK sample draw, and where feasible, it was preferable that subjects remained at the study center until after end-of-study assessment on Day 3.

Number of Subjects (planned and analyzed): Thirty-six subjects between the ages of 12 and 17 years (up to 17 years 364 days), inclusive were planned to be enrolled in the study. Thirty-eight subjects were analyzed for safety, tolerability, and PK.

Diagnosis and Main Criteria for Inclusion: Men or women between 12 and 17 years (up to 17 years 364 days) of age, inclusive, with weight at least 30 kg, and medically confirmed need for control of pain due to injury or nonmalignant disease. Subjects with known allergy to the study drug, excipients of the formulation or other opioids were to be excluded from participating in the study.

Test Product, Dose and Mode of Administration, Batch No.: ULTRAM ER was supplied as 25 mg tablets (Batch number 29410407, expiration date 30 April 2008) and 50 mg tablets **(**Batch number 29420407, expiration date 30 April 2008). Study drug was administered on Day 1 with approximately 240 mL of water, apple or berry juice.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable

Duration of Treatment: The total study length, including screening, treatment, and end-of-study evaluation for each subject, was approximately 24 days.

Criteria for Evaluation:

Pharmacokinetics: Serial blood samples for plasma concentration determination of racemic tramadol, racemic M1, racemic M5 metabolites and of the (+) and (-) enantiomers of tramadol, M1, and M5 were collected predose and at 1-, 4-, 6-, 8-, 12-, 16-, 24-, 36-, and 48-hours postdose. Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{∞}, AUC_{last}, $t_{1/2,\lambda}$, λ_z, CL/F, and Vd/F) and were estimated by model independent methods. The primary variable of the study was the AUC_{∞} value of racemic tramadol. Secondary PK variables include other PK parameters (including C_{max}, t_{max}, AUC_{last}, CL/F, Vd/F, and $t_{1/2}$ of racemic tramadol and AUC_{∞}, AUC_{last}, C_{max}, t_{max}, and $t_{1/2}$ of racemic M1 and M5 metabolites).

Tolerability: Tolerability was assessed for 48-hours postdose by nondirect questioning. Tolerability comments were documented in the case report form (CRF).

Safety: Safety including monitoring of adverse events (AEs), clinical laboratory results, physical examination, vital signs, and electrocardiogram (ECG) measurements, were evaluated continuously throughout the study.

Pharmacogenomics: A pharmacogenomic blood sample (5 mL) was collected to allow for genotyping of cytochrome P450 2D6 (CYP2D6) polymorphisms. Participation in pharmacogenomic research was optional. Blood samples were to be analyzed if there were irregularities in the PK results that appeared to be consistent with the CYP2D6 variation.

Statistical Methods: Based on estimates of intersubject PK parameter variability the sample size for this study was considered appropriate to meet the primary study objectives. The intersubject coefficient of variation for AUC_{∞} and C_{max} was estimated to be 45% in the adult population. Assuming the same variability for adolescents, a sample size of 33 pediatric subjects was considered sufficient to achieve 90% power to detect a 30% difference in mean AUC_{∞} between pediatric and adult subjects, using a 2-sided 1-sample t-test at the 5% significance level.

Pharmacokinetics: The primary PK parameter (AUC_{∞}) was compared with historical data from adults using a 1-sample t-test. Log-transformed, dose-and weight-normalized values were used for this comparison. The geometric mean ratio and corresponding 90% confidence interval (CI) of AUC_{∞} were calculated for pediatric versus adult data. Plasma concentration profiles of racemic tramadol, the (+) and (-) enantiomers of tramadol, racemic M1 and racemic M5 and the (+) and (-) enantiomers of M1 and M5 metabolites for each subject were tabulated and plotted. In addition, the plasma concentration data for each collection time and the PK parameters C_{max}, t_{max}, AUC_{last}, AUC_{∞}, CL/F, Vd/F, and $t_{1/2}$ were listed and summarized using descriptive statistics by group. Corresponding 95% CIs were

estimated for the calculated PK parameters (including C_{max}, t_{max}, AUC_{last}, CL/F, Vd/F, and $t_{1/2}$ of racemic tramadol, and AUC_{∞}, C_{max}, t_{max}, AUC_{last}, and $t_{1/2}$ for racemic M1 and racemic M5 metabolites) in the pediatric subjects.

Tolerability: The comments were summarized by subject.

Safety: Data were summarized for all subjects and each group using descriptive statistics. Baseline for all laboratory evaluations, vital signs, and ECG measurements was defined as the last evaluation done before the first study drug administration. Descriptive statistics were calculated for each laboratory analyte and vital signs at baseline and at each scheduled time point. Results of physical examinations were listed.

RESULTS:

A total of 38 adolescents (17 males and 21 females), between 12 and 17 years of age (up to 17 years 364 days), inclusive, received the study drug; 6 subjects received 2.0 mg/kg of ULTRAM ER (hereafter referred to as 2-mg/kg dose group), and 32 subjects received 2.7 mg/kg of ULTRAM ER (hereafter referred to as 2.7-mg/kg dose group).

The demographic and baseline characteristics of subjects enrolled in the 2 dose groups were consistent with the inclusion and exclusion criteria described in the protocol.

PHARMACOKINETIC RESULTS

In this adolescent population tramadol was gradually absorbed after dosing of ULTRAM ER, with tramadol and metabolite M1 reaching median peak concentrations at 12 hours for tramadol and 14 hours for M1 for the 2.0-mg/kg dose (Part 1), and 12 hours for the 2.7-mg/kg dose for both compounds. Metabolite M5 reached median peak concentrations at 16 hours for 2.0-mg/kg group and 12 hours for 2.7-mg/kg dose group. The concentration of tramadol, M1 and M5 declined in a mono-exponential manner. The mean $t_{½}$ of tramadol was 9.7 hours and 8.6 hours for the 2.0-mg/kg and 2.7-mg/kg dose groups, respectively. The mean $t_{½}$ of M1 was 12.4 hours and 10.2 hours for the 2.0-mg/kg and 2.7-mg/kg dose groups, respectively. The $t_{½}$ for M5 was evaluable for only 1 subject in the 2.0-mg/kg group, and 8 subjects in the 2.7-mg/kg group. The mean $t_{½}$ for the 8 subjects in the 2.7-mg/kg group was 12.5 hours.

The geometric means along with 95% CIs for dose- and weight-normalized composite (both 2.0-mg/kg and 2.7-mg/kg groups) AUC_{∞}, AUC_{last}, and C_{max} of tramadol, M1 and M5 are presented in the Table 1 below.

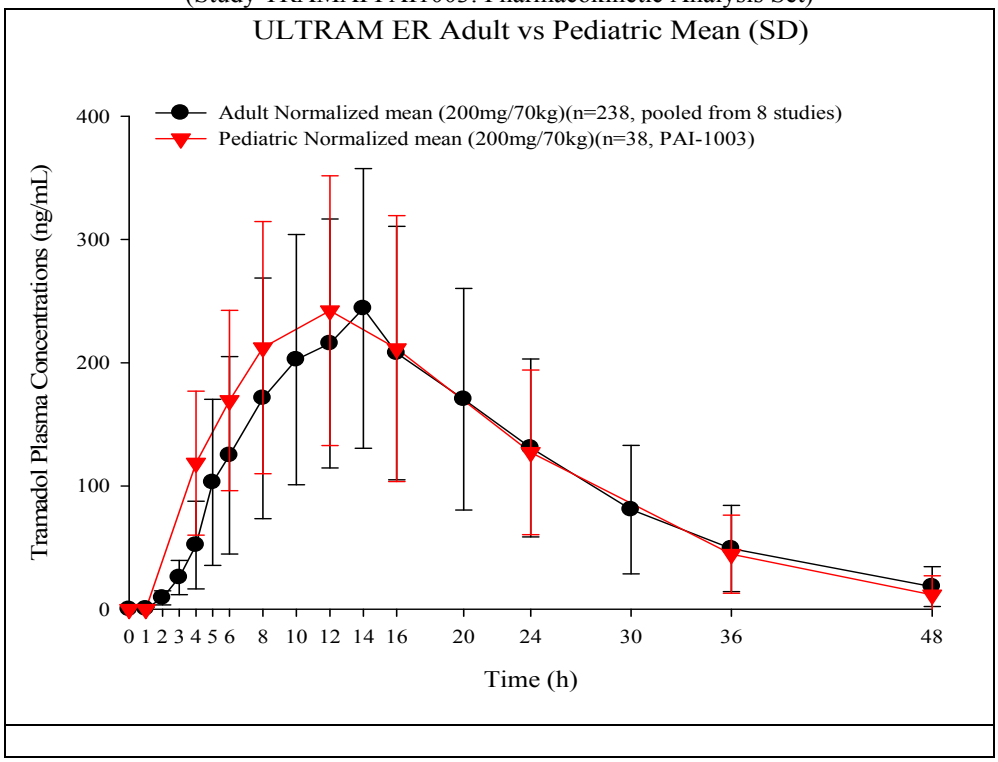
Table 1: Pharmacokinetic Analysis: Geometric Means and 95% Confidence Intervals
(Study TRAMAPPAI1003: Pharmacokinetic Analysis Set)

Substance	PK Parameter	N	LSM (Original Scale)	95% CI
M1	AUCinf	27	23.99	(19.38; 29.69)
	AUClast	36	17.90	(14.68; 21.82)
	Cmax	36	0.99	(0.84; 1.17)
M5	AUCinf	5	9.61	(5.26; 17.55)
	AUClast	36	3.42	(2.48; 4.72)
	Cmax	36	0.31	(0.25; 0.38)
Tramadol	AUCinf	33	73.11	(60.78; 87.95)
	AUClast	38	65.42	(55.11; 77.67)
	Cmax	38	3.20	(2.71; 3.78)

(1) Data were analyzed on natural log scale, but results were back-transformed to original scale
(2) PK parameter values were dose-normalized to 200 mg and weight-normalized to 1 kg
LSM = Least Squares Mean
rpkpar51_t2.rtf generated by rpkpar51.sas.

The comparison of the pediatric PK data to historical adult PK data is limited to racemic tramadol concentrations. A comparison of weight- (70 kg) and dose- (200 mg) normalized pediatric plasma profiles to adult plasma profiles is presented in the Figure 1 below:

Figure 1: Mean Plasma Concentration-Time profile of Tramadol
(Study TRAMAPPAI1003: Pharmacokinetic Analysis Set)



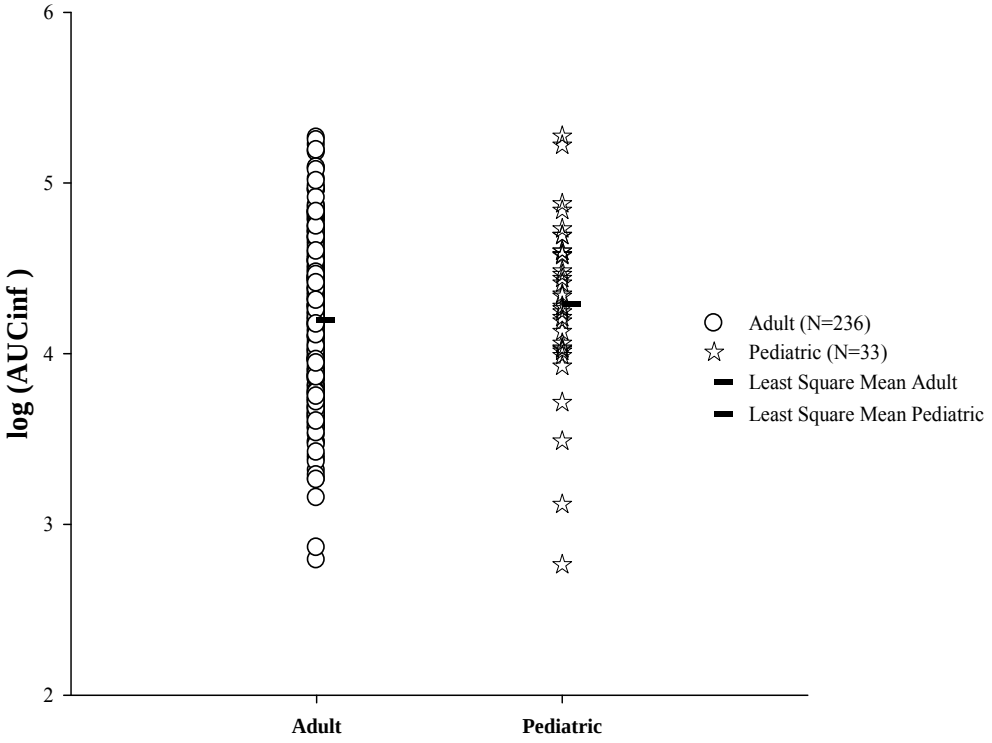
The results of statistical comparison of AUC_{∞} of tramadol, between pediatric and historical adult data are presented in the Table 2, and the comparative data are graphically displayed in the Figure 2 below.

Table 2: Primary Pharmacokinetic Analysis: Comparison of AUC_{inf} of Tramadol between pediatric and adult group
(Study TRAMAPPAI1003: Pharmacokinetic Analysis Set)

Substance	PK Parameter	N	Estimated Ratio (%)	90% CI	P-value
Tramadol	AUCinf	33	109.85	(94.21;128.10)	0.3079

(1) Data were analyzed on natural log scale, but results were back-transformed to original scale
(2) PK parameter values were dose-normalized to 200 mg and weight-normalized to 1 kg
(3) The adult geometric mean used in the analysis equals 66.531 ng*h/mL
rpkpar51_t1.rtf generated by rpkpar51.sas.

Figure 2: Primary Pharmacokinetic Analysis: Comparison of AUC_{inf} of Tramadol between pediatric and adult group: Graphical presentation
(Study TRAMAPPAI1003: Pharmacokinetic Analysis Set)



Note: AUC_{inf} is dose-normalized to 200 mg and weight-normalized to 1 kg.

The estimated geometric mean ratio of adolescent versus adult dose- and weight-normalized AUC_{∞} was 110% with corresponding 90% CI of (94%; 128%). This 90% CI is contained within 77% to 130%. Therefore, it is inferred that the difference between the adolescent and adult populations for dose- and weight-normalized AUC_{∞} is ≤ 30% with 90% confidence. The p-value equals 0.3079.

Based on the comparability of the dose- and weight-normalized mean concentration-time profiles (Figure 1) and the statistical analysis of dose- and weight-normalized AUC_{∞} for the single dose PK of tramadol in children of this age group from the pediatric study to that of adults (where the point estimate of the ratio of geometric means was 110% with a 90% confidence of 94% to 128%), it can be noted that the difference in rate and extent of exposure to tramadol is ≤30% and therefore not clinically relevant.

PHARMACOGENOMIC RESULTS:

The pharmacogenomic results are provided in a separate report.

SAFETY RESULTS:

There were no deaths, serious adverse events or any other significant AEs reported in the study.

A total of 18 (47%) subjects, 6 (100%) from the 2-mg dose group, and 12 (38%) from the 2.7-mg dose group experienced at least 1 treatment-emergent adverse event.

Adverse events most frequently reported by body system were nervous system disorders (13 [34%] subjects), followed by gastrointestinal disorders (11 [29%] subjects). The most common AEs (observed in >5% subjects) were headache (26%), nausea (21%), dizziness (11%), and stomach discomfort (8%).

The majority of the AEs were mild or moderate in severity (except for 1 AE of vomiting reported in Subject 00190562 [2.7-mg dose group], which was severe) and were considered possibly related to study drug administration by the investigator.

There were no clinically relevant treatment-related abnormalities observed in the clinical laboratory tests.

There were no clinically relevant changes or dose-related trends noted in vital signs and physical examinations.

There was no indication of any treatment-related trends noted in the 12-lead ECG parameters.

Tolerability

Two subjects from the 2.7-mg dose group reported nausea, 1 subject (2.7-mg dose group) reported headache, 1 subject from the 2-mg dose group reported feeling 'hyped up', and 1 subject from the 2-mg dose group reported feeling drowsy, all of which were reported as AEs.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION:

- Single dose racemic tramadol concentrations after oral administration of ULTRAM ER in adolescent subjects 12 to 17 years of age were similar to those observed in adults.
- Based on dose normalized to body weight (DN) AUC_{last}, exposure to the active metabolite M1 was about 30% lower in subjects 12 to 17 years of age compared with adult subjects. Given with a similar distribution pattern of M1 to tramadol AUC ratio between the pediatric population and a large adult population, the impact of this finding on the efficacy of tramadol is unlikely to be clinically significant.
- Based on DN AUC_{last} the exposure to the non-active metabolite M5 after administration of Ultram ER was about 70% lower than in subjects 12 to 17 years of age compared with adults. This finding is unlikely to be of clinical significance.
- Single oral doses of 2 mg/kg of ULTRAM ER and 2.7 mg/kg of ULTRAM ER were well tolerated by adolescents between 12 and 17 years old, inclusive.
- The most commonly reported TEAEs (occurring in >5% of subjects), were headache, dizziness, nausea, and stomach discomfort.
- There were no consistent posttreatment- or time-related changes for any safety parameters (vital signs, ECGs, and clinical laboratory evaluations) in subjects who received either 2 mg of ULTRAM ER or 2.7 mg of ULTRAM ER.

Disclaimer

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