SYNOPSIS

Name of Sponsor/Company	Janssen Korea Ltd.
Name of Finished Product	ULTRACET® ER
Name of Active Ingredient(s)	Tramadol HCl 75 mg/Paracetamol (Acetaminophen) 650 mg Tramadol HCl 75 mg/Paracetamol (Acetaminophen) 650 mg)

Status: Approved

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Prepared by: Janssen Korea Ltd.

Protocol No.: TRAMCTPAI1003

Title of Study: A Single-Dose, Open-Label, Randomized, Two-Way Crossover Pivotal Study to Assess the Bioequivalence of a New ULTRACET ® ER Tablet With Respect to a Marketed ULTRACET ® ER Tablet Under Fasted Conditions

NCT No.: NCT01778075

Clinical Registry No.: CR100924, TRAMCTPAI1003

Principal Investigator: In-Jin Jang, MD. PhD, Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, Seoul, Korea

Study Center(s): Seoul National University Hospital

Publication (Reference): None

Study Period: 03 January 2013 through 06 February 2013. Database lock occurred on 15 April 2013.

Phase of Development: 1

Objectives: The primary objective of the study was to evaluate the bioequivalence of 2 Ultracet ER (extended release) combination tablet formulations of tramadol hydrochloride and acetaminophen (APAP): one, the currently marketed tablet (hereafter referred to as the “Marketed Ultracet ER”) and the other, the same tablet formulation using an optimized manufacturing process (hereafter referred to as the “New Ultracet ER”). The study was conducted in a healthy population under fasted conditions. The secondary objective was to evaluate the overall safety of the subjects throughout the study.

Methodology: Randomized, open-label, single-center, two-period crossover study in healthy adult subjects. Each subject was randomly assigned to 1 of 2 treatment sequences on Day -1 of Period 1, prior to the first dose of study drug. Specific evaluations and their timings can be found in the Time and Events Schedule that follows the protocol synopsis.

Number of Subjects (planned and analyzed): A total of 56 subjects were planned to be enrolled in this study to ensure that 52 subjects complete all study procedures, including the 48-hour pharmacokinetic (PK) blood sample collections, and the end-of-study evaluations.

Treatment Assignment

Sequence	Subjects	Period 1	Period 2
A	28	New Ultracet ER	Marketed Ultracet ER
B	28	Marketed Ultracet ER:	New Ultracet ER

Actual number of treated subjects: New Ultracet ER (56) Marketed Ultracet ER (54)

Analysis Populations

	Total (N=56) n (%)
Planned	56 (100)
Enrolled	56 (100)
Randomized	56 (100)
Safety population	56 (100)
PK population	54 (96.4)

NOTE: Safety population includes all randomized subjects who received at least 1 dose of study drug.

Criteria for Inclusion: Healthy adult men between 20 and 55 years of age, inclusive, body mass index (BMI) between 18.5 and 30 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 the New Ultracet ER administered under fasted conditions. The New Ultracet ER was identical in formulation to the Marketed Ultracet ER, but was prepared using an optimized manufacturing process. Registration Batch No. JS355

Reference Therapy, Dose and Mode of Administration, Batch No.: Single oral dose of the Marketed Ultracet ER administered under fasted conditions. Commercial Batch No. 15817

Duration of Treatment: This study consisted of a screening phase (within 2 to 21 days before the first administration of study drug) followed by an open-label treatment phase consisting of 2 treatment periods, each 4 days in duration (Day -1 to Day 3). Successive study drug administration was to be separated by a washout period of 7 days (which is greater than 5 times the half-lives of the 2 drug components) from the first dose of study drug in each period. The total study duration was between 5 weeks and 7 weeks (including the screening and end-of-study visits).

Criteria for Evaluation:

Pharmacokinetics

During the open-label treatment phase, serial blood samples for the determination of plasma concentrations of racemic tramadol and APAP were collected before and up to 48 hours following the administration of study drug on Day 1. The following plasma pharmacokinetic parameters were calculated: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2}$. Analysis was done for each analyte separately.

Safety

Safety was evaluated throughout the study (see the Time and Events Schedule of the protocol for details) by examining the incidence and type of adverse events (AEs), and changes in clinical laboratory test values, physical examination results, serial vital sign measurements and 12-lead ECGs from the screening phase through study completion, including the washout interval.

Statistical Methods:

Sample Size Determination

Using a conservative estimate of 30% for intrasubject coefficient of variation and a 5% level of significance, a sample size of 52 subjects was considered sufficient to conclude bioequivalence between treatment A (single oral dose of New ULTRACET ER) and. treatment B (single oral dose of Marketed ULTRACET ER) with 90% power when the 2 treatment means differ by 5%. The overall power for both analytes (racemic tramadol and APAP) was 80%.

Pharmacokinetics

For all subjects, individual and mean plasma concentration versus time profiles for each treatment and each analyte were plotted. Plasma concentration data at each time point were summarized with mean, standard deviation and coefficient of variation for each treatment. All estimated PK parameters were summarized with arithmetic mean, median, geometric mean, minimum, maximum, standard deviation, and coefficient of variation for each treatment and each analyte.

For each treatment, descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, geometric mean, median, minimum, and maximum were calculated for racemic tramadol and APAP plasma concentrations at each sampling time and for all PK parameters racemic tramadol and APAP.

The primary PK parameters of interest for the statistical analysis were AUC_{last}, AUC_{∞}, and C_{max} of racemic tramadol and APAP. The analyses were performed on log-transformed estimated PK parameters. Only the data from subjects who completed the study were included in the statistical analysis. If a PK parameter of interest was not estimable for a given subject in 1 or more periods, the subject's data was not included in the statistical analysis of that particular parameter. Mixed effects models were fit to the data with the logarithm of AUC_{last} and AUC_{∞} as the dependent variable, treatment-sequence group, period, and treatment (A, B) as fixed effects, and subject as a random effect. The estimated least squares means and intrasubject variance from the mixed effects model were used to construct 90% confidence intervals for the differences in means on a log scale for A vs. B treatments.

Ninety percent confidence intervals for the ratio of mean values of AUC and C_{max} of racemic tramadol and APAP of Treatments A and B were constructed using the estimated least squares means and intrasubject variance from a mixed-effects model. Treatments A and B were to be considered bioequivalent if the 90% confidence intervals for the ratio of the geometric means (A/B) of racemic tramadol and APAP fall within 80% to 125%.

Safety

All subjects who were randomly assigned to a treatment sequence and received at least one dose of the study drug were included in the safety and tolerability analyses. 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:

STUDY POPULATION:

A total of 75 healthy subjects were screened, and 56 eligible subjects were randomized and enrolled. Of the 56 randomized subjects, 54 completed the study and 2 discontinued prematurely. Subject 18 was discontinued because of vomiting within 24 hours after first drug administration. Subject 28 was discontinued due to an AE (herpes zoster infection) after study drug administration in Period 1.

PHARMACOKINETIC RESULTS:

To compare the PK of APAP and tramadol between the 2 treatment groups, point estimates and 90% CIs of the geometric mean ratios (New Ultracet ER / Marketed Ultracet ER) for C_{max}, AUC_{last} and AUC_{inf} were determined by analysis of variance (ANOVA) using a mixed effect model considering the sequence, period, and treatment. The point estimates (90% CIs) of the geometric mean ratio of the C_{max}, AUC_{last} and AUC_{inf} for APAP were 1.04 (0.99 – 1.10) , 1.01 (0.99 – 1.02) and 1.01 (0.99 – 1.02), respectively, while those for tramadol were 1.04 (1.01 – 1.07), 1.02 (0.99 – 1.04) and 1.02 (0.99 – 1.04), respectively.

Tramadol Pharmacokinetic Parameters by Treatment

Parameter	New Ultracet ER (N=54)		Marketed Ultracet ER (N=54)		90% CI of GMR
	Mean	SD	Mean	SD	
C_{max}(ng/mL)	156.64	34.02	151.43	35.89	1.01-1.07
AUC_{last}(h*ng/mL)	1764.88	639.38	1748.44	679.08	0.99-1.04
AUC_{inf}(h*ng/mL)	1789.87	671.84	1774.09	712.42	0.99-1.04

GMR = Geometric mean ratio

Acetaminophen Pharmacokinetic Parameters by Treatment

Parameter	New Ultracet ER (N=54)		Marketed Ultracet ER (N=54)		90% CI of GMR
	Mean	SD	Mean	SD	
C_{max}(ng/mL)	6044.44	1697.81	5744.82	1494.09	0.99-1.10
AUC_{last}(h*ng/mL)	35413.03	8519.92	35284.41	9052.28	0.99-1.02
AUC_{inf}(h*ng/mL)	36030.38	8634.71	35906.48	9165.45	0.99-1.02

GMR = Geometric mean ratio

SAFETY RESULTS:

After the administration of New Ultracet ER or Marketed Ultracet ER, a total of 26 AEs were reported by 11 out of the 56 subjects. None of them were serious adverse events (SAEs), and all resolved without sequelae. All AEs were mild in severity. The number of subjects with an AE and the number of AEs were similar between the 2 treatments groups.

Summary of Adverse Events

	New Ultracet ER (N=56)		Marketed Ultracet ER (N=54)	
	n	(%)	n	(%)
One or more adverse events	7	(12.5)	6	(11.1)
One or more serious adverse events	0	(0)	0	(0)
Deaths	0	(0)	0	(0)
Treatment stopped due to adverse events	1	(1.8)	0	(0)

No notable study limitations were identified by the sponsor.

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