PriCara, Unit of Ortho-McNeil, Inc.

Clinical Study Report

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Tramadol HCl/Acetaminophen for the Treatment of Painful Diabetic Neuropathy

Protocol CAPSS-237; Phase III

RWJ-26898/RWJ-03465, tramadol HCl/acetaminophen

PRINCIPAL INVESTIGATOR:
Multi-center, 46 Investigators

DATE STUDY INITIATED:
23 January 2004

DATE STUDY COMPLETED:
3 May 2005

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

Confidentiality Statement

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SYNOPSIS

NAME OF SPONSOR/COMPANY: PriCara, Unit of Ortho-McNeil, Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: ULTRACET® (tramadol HCl with acetaminophen) NAME OF ACTIVE INGREDIENT(S): (±)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride *N*-acetyl-*p*-aminophenol	Volume: Page:	
Protocol No.: CAPSS-237 **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Tramadol HCl/Acetaminophen for the Treatment of Painful Diabetic Neuropathy		
Principal Investigator: Multicenter, 46 investigators		
Publication (Reference): None		
Study Initiation/Completion Dates: 23 Jan 2004 to 3 May 2005		**Phase of development:** 3
Objective: The objective of this study was to compare the analgesic efficacy and safety of tramadol HCl/acetaminophen versus placebo for the treatment of painful diabetic neuropathy.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study. Approximately 300 subjects aged 18 to 75 years, who were experiencing painful diabetic neuropathy, were to be enrolled. The study consisted of 3 phases: Screening, Double-Blind, and Taper/Exit. Subjects were randomized equally to treatment with tramadol HCl/acetaminophen or placebo. The Screening Phase lasted up to 28 days and consisted of 2 periods (Washout and Baseline). The Washout Period (Visit 1) lasted up to 3 weeks during which time subjects were instructed to discontinue any medication prohibited by the protocol. Subjects who had washed out of all disallowed medication for the required time returned to the study site and entered the Baseline Period (Visit 2). Subjects with intolerable pain during the Washout Period were permitted short-acting non-opioid analgesics up to within 24 hours of Visit 2. If a subject continued to experience intolerable pain, he/she could be considered for early entry in the Baseline Period on a case-by-case basis. The Baseline Period lasted for at least 7 days. During this period, subjects were instructed to call into an Interactive Voice Response (IVR) system daily at bedtime to record their average daily pain and average daily sleep interference assessments for the previous 24-hour period. Subjects returned to the study site (Visit 3) for review of their IVR system entries. At Visit 3, subjects who had documented average daily pain assessments for at least 4 of 7 days and had a mean of the average daily pain scores of at least 5 on an 11-point scale (0=no pain to 10=pain as bad as you can imagine) were eligible to enter the Double-Blind Phase of the study, if they continued to meet the entry criteria. Subjects experiencing severe or intolerable pain in the lower extremities during the 7-day Baseline Period were considered for early entry into the Double-Blind Phase on a case-by-case basis. No supplemental analgesic medication was permitted during the Baseline Period. The Double-Blind Phase consisted of 2 periods: Titration and Maintenance. The Double-Blind Phase lasted approximately 66 days (10-day titration; 8-week maintenance). Subjects were randomized equally in a double-blind fashion to 1 of 2 treatment groups; tramadol HCl/acetaminophen or placebo. During the Titration Period, study medication was titrated according to the protocol recommended schedule up to a maximum of 1-2 tablets (37.5 mg tramadol HCl/325 mg acetaminophen or placebo) q.i.d not to exceed 8 tablets (300 mg tramadol HCl/2600 mg acetaminophen or placebo) per 24-hour period. During the Titration Period, subjects were permitted to take Tylenol® Extra-Strength (500 mg caplets), as supplemental analgesic medication. A subject could take up to a maximum of 4 caplets daily, provided the subject was taking no more than 6 tablets of study medication daily so that the total daily dose of acetaminophen did not exceed 4000 mg. No supplemental analgesic medication was permitted from within 24 hours of Visit 4 (end of Titration Period) through to the end of the Double-Blind Phase of		

SYNOPSIS (CONTINUED)

the study. During the Double-Blind Phase, subjects were instructed to call into the IVR system every night at bedtime to record their average daily pain, average daily sleep interference, and the number of study medication tablets taken in the previous 24-hour period. Study visits during the Titration Period occurred on Day 1 (Visit 3) and Day 10 (Visit 4). Subjects were required to be taking a minimum of 2 tablets of study medication per day to enter the Maintenance Period.

The Maintenance Period lasted 56 days (8 weeks). Study visits during the Maintenance Period occurred on Day 38 (Visit 5) and Day 66 (Visit 6). During the Maintenance Period, subjects could have increased their daily dosage of study medication, as needed, up to a maximum of 2 tablets q.i.d., not to exceed 8 tablets (300 mg tramadol HCl/2600 mg acetaminophen or placebo) per 24-hour period. As noted above, supplemental analgesic medication was not permitted during the Maintenance Period.

It was recommended that all subjects taper their study medication upon completion of or discontinuation from the study. The length of the taper was at the discretion of the investigator and varied according to the dose of study medication being taken. Subjects returned to the study site when the tapering was complete for a final visit, Visit 7 (Day 80).

Number of Subjects (planned and analyzed): 300 subjects planned, 313 randomized, 312 evaluated for efficacy and 313 evaluated for safety.

Diagnosis and Main Criteria for Inclusion: To be eligible for inclusion in the study, subjects were to be 18 to 75 years of age, have experienced lower extremity pain due to painful diabetic neuropathy on a daily basis for the previous 3 months, have a documented history of Type I or Type II diabetes mellitus with an HbA_{1C}<10%, be on a stable diabetic regimen for at least 3 months, and have a baseline mean of the average daily pain assessment score of ≥5 on an 11-point scale (0-10).

Test Product, Dose and Mode of Administration, Batch No.: The test product consisted of 37.5 mg tramadol HCl/325 mg acetaminophen tablets (Batch number R-12234) administered orally. Study medication was titrated according to the protocol recommended titration schedule up to a maximum of 2 tablets q.i.d. as needed, not to exceed 8 tablets (300 mg tramadol HCl/2600 mg acetaminophen) per 24-hour period. Subjects were required to be taking a minimum of 2 tablets per day to enter the Maintenance Period of the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was provided in identically appearing tablets (Batch number R-12235) and was administered orally according to the same method as the active study medication.

Duration of Treatment: Subjects received study medication for 66 days during the Double-Blind Phase (10-day Titration Period, 8-week Maintenance Period).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the change in the mean of the average daily pain scores reported to the IVR system from baseline to the final week.

Secondary efficacy criteria included the change from baseline in the mean of the average daily pain scores for the Titration Period and for each week of the Maintenance Period, proportion of 30% and 50% responders at final week, time to first week with a 30% and 50% response, change from baseline in the average daily sleep interference scores for the Titration Period, and each week of the Maintenance Period, change from baseline to final and from baseline to each visit for the Pain Visual Analog Scale (VAS) and Brief Pain Inventory Short Form (BPI), change from baseline to final for each Short-Form McGill Pain Questionnaire (SF-MPQ) scale, Profile of Mood States (POMS) scale, Short Form-36 Health Survey (SF-36) subscale and composite score, and distribution of ratings in the Physician Global Impression of Change and Subject Global Impression of Change (PGIC and SGIC) scores.

Safety: Safety evaluations included vital sign (pulse, blood pressure, weight) measurements, physical and neurological exams, clinical laboratory tests (hematology, chemistry, and urinalysis) and the monitoring of adverse events (AEs). Urine pregnancy tests were performed on women of childbearing potential at study entry.

SYNOPSIS (CONTINUED)

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NAME OF FINISHED PRODUCT: ULTRACET® (tramadol HCL with acetaminophen) NAME OF ACTIVE INGREDIENT(S): (±)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride *N*-acetyl-*p*-aminophenol	Volume: Page:	

Statistical Methods:

Efficacy: The Intent-to-Treat (ITT) population was used for all efficacy analyses and included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline efficacy measurement. All statistical tests were conducted at the 2-sided, 5% significance level. The primary efficacy analysis was done on the change in the mean of the average daily pain scores reported to the IVR system from baseline to final week. An analysis of covariance was applied for the treatment comparison of final week mean of the average daily pain scores with baseline mean of the average daily pain as a covariate and treatment and center as qualitative design factors.

Safety: The Evaluable-for-Safety population was used for all safety analyses and included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline safety measure. The number and percentage (%) of subjects reporting AEs were tabulated by treatment group. Listings of subjects reporting serious adverse events (SAEs), and withdrawing due to an AE, were also provided. The number of subjects reporting AEs was tabulated by relationship to study medication as well as by severity. The number of subjects reporting treatment-limiting adverse events (TLAEs) was summarized. AEs were summarized by using the World Health Organization-Adverse Reaction Terminology (WHO-ART) (Version 1992, 3rd Quarter) body system and preferred term.

Changes from baseline in vital signs (pulse, blood pressure and weight), physical examinations, and in clinical laboratory parameters (hematology, chemistry and urinalysis) were assessed. The number and percentage of subjects with markedly abnormal laboratory values and markedly abnormal vital signs were summarized.

SUMMARY

DISPOSITION OF SUBJECTS

Of the 313 subjects in the All Subjects Randomized population, 238 subjects completed the study (129 subjects, 80.6% in the tramadol HCl/acetaminophen group and 109 subjects, 71.2% in the placebo group). The majority of subjects who discontinued early in the placebo group withdrew due to lack of efficacy (23 subjects, 15.0%) compared to 8 subjects, 5.0% in the tramadol HCl/acetaminophen group. The majority of subjects who discontinued early in the tramadol HCl/acetaminophen group withdrew due to TLAEs (13 subjects, 8.1%). The proportion of subjects in the placebo group who discontinued due to TLAEs (10 subjects, 6.5%) was similar to that of the tramadol HCl/acetaminophen group.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

Of the 312 subjects included in the ITT population, 184 (59.0%) were male and 128 (41.0%) were female. The subjects ranged in age from 22 to 76 years (mean age 55.7 years). The majority of subjects were white (241 subjects, 77.2%). Thirty-five subjects (11.2%) were black, and 30 subjects (9.6%) were Hispanic. The majority of subjects (292, 93.6%) had a diagnosis of Type II diabetes and the baseline mean of the average daily pain score was 7.12. There were no clinical differences in demographic or baseline characteristics between treatment groups.

SYNOPSIS (CONTINUED)

EFFICACY RESULTS:

Tramadol HCl/acetaminophen was statistically superior compared to placebo for the primary efficacy variable, the change in the mean of the average daily pain scores from baseline to final week (p=0.001).

Tramadol HCl/acetaminophen was also statistically superior to placebo for the majority of secondary efficacy variables. The proportion of 30% and 50% responders to treatment at final week was significantly greater for the tramadol HCl/acetaminophen group compared to placebo (p=0.001 and p=0.003, respectively). Likewise, the time to first week with a 30% and 50% response (e.g., the final day of the week in which a subject became a responder, Day 10 if 50% reduction occurred during titration, Day 17 if 50% reduction occurred during Week 2) was significantly shorter for the tramadol HCl/acetaminophen group compared to placebo (p=0.001 for both). The median time to a 30% response was Week 3 for the tramadol HCl/acetaminophen group and Week 7 for the placebo group. The median time to a 50% response was Week 7 for the tramadol HCl/acetaminophen group and was not achieved for the placebo group. Subjects in the tramadol HCl/acetaminophen group had a significantly greater reduction in pain as measured by the VAS compared to subjects in the placebo group (p<0.001) and a greater reduction in the mean of average daily sleep interference from baseline to final week (p=0.001).

Tramadol HCl/acetaminophen was statistically superior to placebo for the majority of subscales on the efficacy questionnaires (BPI, SF-MPQ, POMS, and SF-36). Tramadol HCl/acetaminophen was statistically superior to placebo for all subscales of the BPI: least pain, pain "right now," pain relief, and pain interference (p=0.001); worst pain (p=0.001); and average pain (p=0.004). On the SF-MPQ, tramadol HCl/acetaminophen was statistically superior to placebo for the sensory pain (11.3 vs. 12.6, p=0.008), total pain (14.0 vs. 15.7, p=0.013), and Present Pain Index (PPI) (1.4 vs. 1.8, p<0.001) subscales. Tramadol HCl/acetaminophen was numerically superior to placebo for the affective pain subscale, however, the difference was not statistically significant (2.7 vs. 3.1, p=0.090). Tramadol HCl/acetaminophen was statistically superior to placebo for the total mood disturbance scale of the POMS (2.48 vs. 3.39, p=0.047) and for the vigor subscale (1.97 vs. 1.69, p=0.007). Tramadol HCl/acetaminophen was numerically superior to placebo for the remainder of the POMS subscales (tension, depression, anger, fatigue, and confusion), however, the differences were not statistically significant (p≥0.087). The following SF-36 subscales were significantly in favor of tramadol HCl/acetaminophen: bodily pain (p<0.001), social functioning (p=0.012), and reported health transition (p<0.001). Tramadol HCl/acetaminophen was also numerically superior to placebo for the subscales physical functioning, general health, vitality, mental health, and role-emotional but the differences were not statistically significant (all p's≥0.082). The mental and physical component summaries were not statistically significantly different for the tramadol HCl/acetaminophen group compared with the placebo group, however, the physical component summary trended toward significance (p=0.063)

Overall, both subjects and investigators gave a significantly superior global impression of change for treatment with tramadol HCl/acetaminophen compared to treatment with placebo, based on the PGIC (p<0.001) and SGIC (p<0.001) scores.

SAFETY RESULTS:

Of the 313 subjects in the Evaluable-for-Safety population, 96 subjects (60.0%) in the tramadol HCl/acetaminophen group and 90 subjects (58.8%) in the placebo group experienced AEs. The most common treatment-emergent AEs (TEAEs) in the tramadol HCl/acetaminophen and placebo groups were nausea (11.9 vs. 3.3%), headache (5.6% vs. 7.2%), dizziness (6.3% vs. 1.3%), and somnolence (6.3% vs. 1.3%).

The majority of AEs were mild to moderate in severity. Fifteen subjects (9.4%) in the tramadol HCl/acetaminophen group and 16 subjects (10.5%) in the placebo group experienced AEs that were marked in severity.

Five subjects (3.1%) in the tramadol HCl/acetaminophen group and 5 subjects (3.3%) in the placebo group experienced SAEs. All of the SAEs in both treatment groups were considered by the investigator to be unrelated or of doubtful relationship to study medication. Thirteen subjects (8.1%) in the tramadol HCl/acetaminophen group and 10 subjects (6.5%) in the placebo group discontinued treatment due to an AE. The most common TLAEs in the tramadol HCl/acetaminophen group were nausea (1.9%) and constipation (1.3%). In the placebo group there were no AEs for which more than 1% of subjects discontinued the study.

There were no deaths.

There were no clinically relevant mean changes from baseline in hematology, chemistry, or urinalysis laboratory tests, or in vital signs in either group.

SYNOPSIS (CONTINUED)

Adverse Events Overall Summary

	Tram/APAP (N=160) n	(%)	Placebo (N=153) n	(%)
Number (%) of subjects with any adverse event regardless of relationship to study medication[a,b]	96	(60.0)	90	(58.8)
Number (%) of subjects with any adverse event related to study medication[a,b]	43	(26.9)	26	(17.0)
Number (%) of subjects with any adverse event causing withdrawal from study[c]	13	(8.1)	10	(6.5)
Number (%) of subjects with any serious adverse event[c]	5	(3.1)	5	(3.3)
Number (%) of subjects with any serious adverse event related to study medication[a,c]	0	(0.0)	0	(0.0)
Number (%) of subjects who died	0	(0.0)	0	(0.0)

[a] An event is related if its relationship to study medication is possible, probable or very likely.
[b] Includes adverse events occurring after randomization.
[c] Includes all adverse events.

CONCLUSION:

The results of this study demonstrate that tramadol HCl/acetaminophen is safe and effective for the treatment of painful diabetic neuropathy. Tramadol HCl/acetaminophen showed superior efficacy when compared to placebo for the treatment of peripheral diabetic neuropathy. The safety profile seen in this study is consistent with that previously observed for tramadol HCl/acetaminophen.

Date of the report: 19 December 2005

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