Ortho McNeil Pharmaceutical, Inc.

Clinical Study Report

A Comparison of the Efficacy and Safety of ULTRACET® (Tramadol HCl/Acetaminophen) versus Placebo for the Acute Treatment of Migraine Headache Pain

Protocol CAPSS-223; Phase IV

RWJ-26898-RWJ03465

COORDINATING INVESTIGATOR:
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DATE STUDY INITIATED:
28 April 2003

DATE STUDY COMPLETED:
28 August 2003

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

SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho McNeil Pharmaceutical, Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: ULTRACET® **NAME OF ACTIVE INGREDIENT(S):** Tramadol HCl/Acetaminophen	**Volume:** **Page:**	
Protocol No.: CAPSS-223 **Title of Study:** A Comparison of the Efficacy and Safety of ULTRACET® (Tramadol HCl/Acetaminophen) versus Placebo for the Acute Treatment of Migraine Headache Pain		
Coordinating Investigator: Stephen Silberstein, MD - Jefferson Headache Center, Philadelphia, PA; USA		
Publication (Reference): None		
Study Initiation/Completion Dates: First patient in: 28 April 2003 Last patient out: 28 August 2003		**Phase of development:** 4
Objectives: The objective of this study was to evaluate the efficacy and safety of ULTRACET® (37.5 mg tramadol HCl/325 mg acetaminophen) as compared to placebo for the acute treatment of pain associated with migraine headache.		
Study Design: This was a multicenter, single-dose, outpatient, randomized, double-blind, placebo-controlled, parallel-group study of approximately 350 subjects, 18 years of age and older, experiencing at least moderate pain associated with migraine headache. The study consisted of 2 phases: screening and double-blind treatment phase. **Screening Phase:** During the Screening phase, subjects who had a history of migraine with or without aura as defined by the International Headache Society (IHS) classification criteria[1] and who met entry criteria for the study were identified. The study was to be explained and informed consent was to be obtained. Following Visit 1 (Screening/Randomization Visit), eligible subjects were to be randomized in a double-blind fashion in a 1:1 ratio to receive ULTRACET® or placebo (175 subjects per group). Subjects were to have left the investigative center with 1 dose (2 tablets) of blinded study medication, a timing device, and a subject diary. Subjects were not to have treated a headache that was present upon awakening, and the headache must not have spontaneously improved since its onset. The subject was to be migraine-free for 48 hours prior to the targeted headache; must not have taken any excluded medications within 48 hours of dosing with study medication; and if taking an allowable prophylactic migraine medication, was required to be on a stable dose for 6 weeks prior to study entry and to remain on a stable dose for the duration of the study. Subjects were not to treat their headache with coffee/tea/caffeine or topical treatment with ice or balms within the first 2 hours after dosing with study medication. **Double-Blind Treatment Phase:** After the occurrence of a migraine headache of at least moderate intensity (on a scale of no pain, mild, moderate, or severe pain), typical of their usual migraine pattern, subjects were to have self-administered the study medication. Efficacy and safety were to be assessed at 0.5, 1, 2, 3, 4, and 6 hours post-dosing and up to 24 hours post-dosing. Each subject was to have completed the subject diary at baseline and captured the following information about the treated migraine headache: the date and time study medication was taken; pain intensity assessment (moderate, or severe); presence or absence of any aura associated with the migraine. At baseline and at 0.5, 1, 2, 3, 4 and 6 hours post-dosing, the subject also was to capture the presence of vomiting, the presence and severity (none, mild, moderate, severe) of migraine associated symptoms (nausea, photophobia, phonophobia), and functional disability. At 6 hours and 24 hours post-dosing, or when supplemental pain medication or anti-emetic medication was taken, the subject was to have noted in the subject diary his/her overall (global) impression of the effectiveness of the study medication (SGIC) and the time and pain intensity of the recurrence of migraine headache (up to 24 hours post-dose). Subjects were to have recorded any adverse events that occurred from the time of the first study-related procedure until Visit 2 (Final Visit). Additionally any concomitant medications since Visit 1 were to have been recorded. Treatment with study medication was to have occurred within 30 days of randomization, and within 2 hours of onset with a migraine of at least moderate intensity. Subjects were to have returned to the site for Visit 2 (Final Visit) within 72 hours after dosing with study medication.		

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Diagnosis and Key Criteria for Inclusion:

- Subjects 18 years of age and older, experiencing at least moderate pain associated with a migraine headache;
- Subjects met the IHS criteria for the classification of migraine with or without aura for at least 1 year;
- Subjects who had a migraine headache frequency of at least 1 migraine headache every month and not to exceed 6 migraine headaches per month within the past year;
- Subjects who were able to differentiate a migraine headache from an interval (e.g., tension-type) headache.

Key Criteria for Exclusion

- Subjects who routinely experienced any other type of headache that would confound discrimination from a migraine headache;
- Subjects who had more than 13 headache days per month in the previous 6 months;
- Subjects with onset of migraine after age 50;
- Subjects who took more than 1 allowable prophylactic medication for migraine headache within the last 6 weeks prior to Visit 1;
- Subjects who failed more than 2 adequate trials of an established prophylactic anti-migraine regimen due to lack of efficacy (defined as at least 1 month of treatment at a full therapeutic dose);
- Subjects who used concomitant pain medications on a chronic basis within 30 days of study entry and during the study that may have potentially interfered with efficacy assessments (see Appendix 1.1, Section 8);
- Subjects who had exclusively migraine aura without headache;
- Subjects with headaches related to head or neck trauma;
- Subjects with secondary headaches or headaches due to underlying pathology (i.e., tumor, inflammatory process, hemorrhage, hypertension, etc.);
- Subjects known to have a significantly unstable medical disease;
- Subjects who had a current or recent history, or suspected history, of substance dependence or abuse, or chronic alcohol abuse (with the exception of nicotine or caffeine dependence) within the past 6 months;
- Subjects with incapacitating disability (migraines that usually require bed rest or prohibit performance of daily activity for >50% of the time) during the migraine headaches;
- Subjects who experienced vomiting > 20% of the time during their migraine headaches;
- Subjects who had ophthalmoplegic, chronic (transformed) migraine, cluster headaches, or new onset of basilar or hemiplegic migraines. Subjects who had a history of basilar or hemiplegic migraines were allowed to enroll as long as the symptoms were not long lasting;
- Subjects who had a more painful condition than their migraine pain;
- Subjects who typically had headaches that occur predominately upon awakening;
- Subjects who previously failed tramadol HCl (ULTRAM®) or ULTRACET® therapy, or those who discontinued treatment due to an adverse event;
- Subjects who took tramadol HCl (ULTRAM®) or ULTRACET® within 30 days prior to study entry.

Test Product, Dose and Mode of Administration, Batch No.: ULTRACET® 75 mg tramadol HCl/650 mg acetaminophen) (batch number R12027) was self-administered after the occurrence of a migraine headache of at least moderate intensity.

Reference Therapy, Dose and Mode of Administration, Batch No.: Study medication, consisting of matching placebo in identically-appearing tablets, (batch number R12028) was self-administered after the occurrence of a migraine headache of at least moderate intensity.

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Duration of Treatment: Subjects left the investigative center with 1 dose (2 tablets) of blinded study medication, a timing device, and a subject diary. Treatment with study medication was to occur within 30 days of randomization, and within 2 hours of onset of a migraine of at least moderate intensity. After the occurrence of a migraine headache of at least moderate intensity, which was typical of their usual migraine pattern, subjects administered study medication and recorded in the subject diary the date and time of study medication administration.

Statistical Methods:

The primary efficacy outcome was the response to therapy based on the 2-hour post-dose assessment. A responder was defined as a subject whose pain decreased from severe or moderate, to mild or none with no use of supplemental pain medication or anti-emetic medication at the 2-hour post-dosing assessment. The primary analysis population was the modified intent-to-treat (mITT) population. The modified intent-to-treat (mITT) population is defined as all ITT subjects who met all of the following conditions:

- Subject with a diagnosis that met the IHS criteria for the classification of migraine, with or without aura;
- Headache pain of at least moderate intensity and typical of their usual migraine pattern;
- Treatment within 2 hours of headache onset, headache not present upon awakening, and headache did not spontaneously improve prior to treatment;
- Subject migraine-free for 48 hours prior to the targeted headache;
- Subject did not take any excluded drugs within the 48 hours prior to dosing with study drug;
- Subject did not discontinue, or alter the dose of, their prophylactic migraine medication prior to dosing (if applicable);
- Subject who took the full dose of study medication.

Analyses were also conducted on the intent-to-treat (ITT) population, which was defined as all randomized subjects who took study medication and for whom at least 1 post-randomization and post-dosing efficacy assessment was available. Subjects who do not return their subject diary were not included in the efficacy analysis.

The pain control (response) at 0.5, 1, 2, 3, 4, and 6 hours post-dosing was analyzed with a Cochran-Mantel-Haenszel test, stratified by baseline pain and investigator.

The percentage of subjects who were pain free at 2, 6, and 24 hours post-dosing, were sustained pain free through 24 hours post-dosing, and had sustained improvement through 24 hours post-dosing was analyzed with a Cochran-Mantel-Haenszel test, stratified by baseline pain and investigator. Sustained pain free was defined as subjects who were pain free at the 2-hour post-dosing assessment, and who did not experience a recurrence of moderate or severe headache pain, with no use of supplemental pain medication or anti-emetic medication, up to 24 hours post-dosing. Sustained improvement was defined as a response to therapy at the 2-hour post-dosing assessment (i.e., change in baseline pain intensity from severe or moderate, to mild or none), and retention of response (i.e., pain intensity = 1 [mild] or 0 [none]), with no use of supplemental pain medication or anti-emetic medication up to 24 hours post-dosing. Pain intensity differences from baseline at each time point over 6 hours post-dosing were analyzed with a 3-way analysis of variance (ANOVA) (treatment, baseline pain, and investigator).

The overall impression of the study medication (Subject Global Impression of Change [SGIC]) performed at 6 and 24 hours post dosing was analyzed with an extended Cochran-Mantel-Haenszel test with modified ridit score, stratified by baseline headache pain and investigator.

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Demographics and Baseline Characteristics: A total of 375 subjects were randomized to study treatment. A total of 283 subjects were in the mITT population. Those subjects ranged in age from 19 to 74 years, with a mean age of 39.3 years. The majority of the subjects were White (85.9%) and female (85.9%). The mean baseline pain intensity rating was similar between the treatment groups, with the majority (>73.5%) of subjects reporting moderate pain.

Subject Disposition: The percentage of subjects who completed the study was 83.0% (156) in the ULTRACET® group and 81.8% (153) in the placebo group. Thirty-two subjects in the ULTRACET® group (17%) and 34 subjects in the placebo group (18.2%) discontinued double-blind treatment phase prematurely. The most common reason for premature discontinuation from the study in both treatment groups was "no headache treated" (11.7% and 13.9% of subjects in the ULTRACET® and placebo groups, respectively). These subjects did not experience a headache that met the criteria for treatment.

SUMMARY-CONCLUSIONS

Efficacy Results:

The proportion of migraine responders in the ULTRACET® group was 56.6% compared with 33.3% in the placebo group. Treatment with ULTRACET® was statistically significantly more effective than placebo in reducing migraine pain at 2 hours post-dosing ($P<0.001$). Pain control (response) over time was statistically significantly in favor of ULTRACET®. The ULTRACET® group had a statistically significant ($P<0.026$) difference in pain control compared to the placebo group as early as the 1-hour time point and remained significant for the 2, 3, 4, and 6-hour time points ($P<0.001$).

The proportion of subjects who remained migraine pain free, without the use of supplemental pain or anti-emetic medication, 2 hours, 6 hours, and 24 hours post-dosing was statistically significantly ($P\leq0.013$) greater in the ULTRACET® group compared with the placebo group. A statistically significant difference in pain intensity difference (PID) scores in favor of the ULTRACET® group was observed as early as the 2-hour time point ($P<0.001$). The difference remained statistically significant at each subsequent time point ($P<0.001$).

The migraine-associated symptoms of phonophobia and photophobia were statistically significantly reduced in the ULTRACET® group with phonophobia/photophobia present at baseline at the 2- and 3-hour time points ($P\leq0.027$). Subjects in the ULTRACET® group with phonophobia/photophobia present at baseline showed statistically significant improvement in the severity of these symptoms up to the 3-hour post-dosing assessment ($P\leq0.019$). There were no statistically significant differences in frequency or severity of nausea between the 2 treatment groups ($P\geq0.140$).

The difference between the ULTRACET® group and the placebo group in functional disability scores was not statistically significant at any time point. There were no differences between the ULTRACET® group and the placebo group in the frequency or severity of vomiting.

The subject global impression of change was statistically significantly better for the ULTRACET® group compared with the placebo group ($P=0.004$ at 6 hours post-dosing and $P=0.008$ at 24 hours post-dosing).

The number of subjects who were sustained migraine pain-free without the use of supplemental pain or anti-emetic medication up to 24 hours post-dosing was statistically significantly greater in the ULTRACET® group compared with the placebo group ($P=0.016$). The number of subjects who met the criteria for migraine sustained improvement response to therapy and retained their response without the use of supplemental pain or anti-emetic medication up to 24 hours post-dosing was statistically significantly greater in the ULTRACET® group compared with the placebo group ($P=0.003$).

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Efficacy Results (continued):

There was no statistically significant difference observed between the 2 treatment groups in the number of subjects who required supplemental pain or anti-emetic medication up to 2 hours of dosing. However, the number of subjects who used supplemental pain or anti-emetic medication up to 6 hours of dosing was statistically significantly less in the ULTRACET® group compared with the placebo group ($P<0.001$). Additionally, the time to use of supplemental pain medication or anti-emetic medication was statistically significant in favor of the ULTRACET® group compared with the placebo group ($P < 0.001$).

Safety Results:

The most commonly reported AEs in the ULTRACET® group were nausea, dizziness, vomiting, and somnolence. There were no SAEs, discontinuations due to AEs, and no deaths occurred during the course of the study.

CONCLUSIONS:

- ULTRACET® was effective in the treatment of moderate to severe acute pain associated with migraine.
- In this study, treatment with ULTRACET® in subjects with migraine was safe and generally well tolerated.
- Treatment with ULTRACET® was also effective in the reduction of the migraine-associated symptoms of phonophobia and photophobia.

Date of the report: 07 June 2004

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