1 SYNOPSIS

Name of Sponsor/Company: McNeil Consumer & Specialty Pharmaceuticals	***Individual Trial Table Referring to Part of the Dossier:***	***For National Authority Use Only:***
Name of Finished Product: Acetaminophen ER ***Name of Active Ingredient:*** Acetaminophen	***Volume:*** ***Page:***	

Title of Study: A Randomized, Double-Blind Study Evaluating Acetaminophen Extended Release Caplets (3900 mg/day) and Ibuprofen (1200 mg/day) in the Treatment of Post-Race Muscle Soreness

Investigator: Robert S Lipetz, DO

Study Center: Encompass Clinical Research (Spring Valley, CA)

Publication (reference)*:* None currently.

Studied period: 1 month ***Phase of development****:* IV

Date of first enrolment*:* 21 May 2003

Date of last completed*:* 19 June 2003

Objective: The primary objective is to compare the efficacy of acetaminophen extended release (ER) caplets and ibuprofen in relieving the muscle soreness that occurs after a marathon.

The secondary objective is to compare the safety of acetaminophen ER to ibuprofen in subjects experiencing muscle soreness after a marathon.

Methodology: A phase IV, randomized, double-blind, parallel group study of subjects 18 years of age and older, who completed a marathon and who experienced muscle soreness rated at least 4 on a zero to 10 points scale on the evening after the marathon.

Number of subjects (planned and analyzed): The sample size estimate for this study was based on a relative effect size. A non-inferiority boundary for this study was set as an effect size of 0.35 where effect size was defined as the difference between the non-inferiority limit and the expected difference for the two groups (i.e., zero) divided by the common standard deviation.

Using an effect size of 0.35, it was estimated that 100 subjects per treatment would provide 80% power to reject the null hypothesis that acetaminophen is inferior to ibuprofen at a one-sided alpha level of 0.05, and if 800 subjects were screened approximately 500 subjects would be eligible for randomization and approximately 200 subjects for the Per Protocol analysis.

A total of 497 subjects were randomly assigned to treatment, 483 received study treatment and were included in the Safety Population, 476 were considered eligible, and 377 were included in the Per Protocol population. Protocol violations were the only reason for exclusion of randomized subjects from the Per Protocol population (120 subjects), the most common protocol violation being using less than 80% of the study medication, 99 subjects (19.9%), and not reporting a muscle soreness of at least 4 at baseline (i.e., ineligible), 21 subjects (4.2%).

Diagnosis and main criteria for inclusion*:* Male and female subjects were reviewed for eligibility at the screening visit, and again at the randomization (race day) visit. Subjects were eligible at screening if they were 18 years of age or older; non-pregnant, non-lactating female using an acceptable form of contraception; able to comply with the study visit schedule and conditions of use of the medication; able to swallow the study medication; and willing to provide written informed consent. Subjects were ineligible at screening if they had a previous diagnosis of osteoarthritis requiring analgesic therapy; other major concurrent medical illness; a history of cardiovascular disease, heat injury, or collapse during a running or endurance event; or known hypersensitivity to the study medications.

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Subjects were eligible at the randomization visit if they had completed the marathon; had not used prescription analgesics or other medications that could confound efficacy for at least 1 day or 5 half lives before the marathon; and had not used OTC analgesics during the race. Subjects were ineligible at the randomization visit if they appeared to need medical attention for any reason.

Test product and dosing: Acetaminophen ER, administered orally, 1300 mg, three times per day (3900 mg/day), for five days. Batch number: Z4570

Duration of Treatment: 5 days

Reference therapy, dose and mode of administration, batch number: Ibuprofen, administered orally, 400 mg, three times per day (1200 mg/day), for five days. Batch number: Z4571

Criteria for evaluation:

Efficacy:

Primary variable

- Average change in muscle soreness from baseline for both morning and evening assessments.

Secondary variables

- Average change in muscle soreness from baseline for morning assessments
- Average change in muscle soreness from baseline for evening assessments
- Average ratings of interference with sleep
- Average interference with morning activity
- Average interference with the ability to go for a run
- Time it takes for subjects to report no interference with the ability to go for a run
- Overall satisfaction with treatment

Safety

Safety variables were physical examination (including vitals and weight), urine pregnancy test for female subjects, concomitant medications, and adverse events.

Statistical methods*:*

All primary and secondary analyses were performed using the Per Protocol population.

All primary and secondary variables were summarized by time point and overall for each treatment group separately and pooled over both arms. Summary statistics were presented for the primary and secondary variables by the following subpopulations of the Per Protocol Population, subject took an OTC analgesic prior to marathon, subject did not take an OTC analgesic prior to marathon.

For the primary efficacy endpoint, and all secondary efficacy endpoints with the exception of ability to go for a run, two hypotheses were tested using a step-down approach. The first null hypothesis (H_{01}) was that acetaminophen ER would be no different from ibuprofen versus the alternate (H_{A1}) that it would be superior to ibuprofen. This hypothesis was tested using an ANCOVA model including terms for treatment, baseline muscle soreness, and pre-dose (whether the subject took an OTC analgesic prior to the marathon). The interaction term pre-dose*treatment was not found significant at the 10% level and was removed from all models. Adjusted means by treatment are presented as well as an estimate of the difference between adjusted means. The difference in adjusted means was tested by a one-sided t-test at the 0.05 alpha level.

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If H_{01} was not rejected, a second null hypothesis (H_{02}) was evaluated that acetaminophen ER would be inferior to ibuprofen versus the alternate (H_{A2}) that it would be non-inferior to ibuprofen. This hypothesis was tested and rejected if a one-sided, 95% confidence interval of the difference in adjusted means did not include the non-inferiority boundary defined as a relative effect size of 0.35.

The measure "first time to no (i.e., zero) interference with the ability to go for a run" was presented for each treatment group separately and pooled over both arms. For each subject the time to no interference was calculated with censoring at last recorded time point. If there was a re-emergence, the calculation went to the time of no interference of this re-emergence.

Efficacy results*:*

The primary efficacy endpoint was the average change in muscle soreness from baseline for both morning and evening assessments. There was no evidence to reject the first hypothesis, that acetaminophen ER was no different from ibuprofen (P=0.0670), while there was evidence to reject the second hypothesis, that acetaminophen ER was inferior to ibuprofen (non-inferiority limit = 0.572, one-sided 95% CI $-\infty$ to 0.464). Therefore acetaminophen ER was neither superior nor inferior to ibuprofen.

Similar results were obtained for the secondary efficacy endpoints average change from baseline for morning assessments, average change from baseline for evening assessments, average interference with sleep, average interference with ability to go for a run, and overall treatment satisfaction. In all cases acetaminophen ER was neither superior nor inferior to ibuprofen.

For the secondary efficacy endpoint average interference with morning activity, there was no evidence to reject the first hypothesis, that acetaminophen was no different from ibuprofen, but there was no evidence against the second hypothesis, that acetaminophen was inferior to ibuprofen. The conclusion was that acetaminophen ER was not superior to ibuprofen and acetaminophen ER was inferior to ibuprofen. Collection of data for this endpoint was affected by an error in the IVRS that reversed the polarity of the scale offered to subjects on Day 1. Three different methods of calculation of the average were used; all produced similar results and the same conclusion.

Safety results:

The majority of the 483 subjects who received study treatment experienced no TEAEs. Twenty-four subjects (5.0%) experienced at least 1 TEAE, 11 subjects (4.5%) in the acetaminophen ER group and 13 subjects (5.4%) in the ibuprofen group. In the acetaminophen ER group, the most common individual TEAEs were nausea, 3 subjects (1.2%), and back pain, 2 subjects (0.8%), while in the ibuprofen group, the only TEAE experienced by more than one subject was dyspepsia, 3 subjects (1.2%).

The majority of these AEs were mild, 19 subjects (3.9%), with 5 subjects (1.0%) experiencing one or more moderate AEs. No subjects experienced severe AEs. The majority of subjects experiencing moderate AEs were in the ibuprofen group, 4 subjects (1.7%). No subjects experienced an SAE.

The most common relationships between AEs and treatment were 'possible', 11 subjects (2.3%), and 'not related', 9 subjects (1.9%), with a comparable profile of relationships for both treatment groups.

Three subjects experienced a TEAE leading to discontinuation, 1 subject in the acetaminophen ER group and 2 subjects in the ibuprofen group.

There was no statistical difference between treatment groups in the number of subjects who experienced a TEAE (P=0.6921), in the intensity of TEAEs (P=0.2021), in the relationship to study

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drug (P=0.8089), or in the number of subjects who experienced an AE leading to discontinuation (P>0.9999).

Conclusion:

Acetaminophen ER was not-inferior to ibuprofen in the treatment of post-race soreness in subjects running a marathon. Both treatments were safe and well tolerated.

Date of the report: 3 May 2004

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