1 SYNOPSIS

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

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

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Publication (reference): None

Study period: ***Phase of Development:*** IV
(date of first enrollment) January 8, 2004
(date of last completed) February 18, 2004

Objective: To compare the efficacy of acetaminophen extended release (ER) to placebo in treating the muscle aching and pain (soreness) that occurs after a marathon.

Methodology: This was a phase IV, randomized, double-blind, placebo-controlled, parallel-group study of subjects 18 years of age and older, who completed a marathon and who experienced muscle aching and pain (soreness) rated at least four on a zero-to-ten point scale. At a screening visit, subjects signed an informed consent and had their potential eligibility assessed with the following assessments: medical history and physical examination (PE), including vital signs and weight; and negative urine pregnancy test for all females of childbearing potential. Subjects also completed the Oswestry Disability Index (ODI).

On race day, subjects reported to the study tent upon completion of the marathon. Upon meeting final eligibility criteria, subjects were randomized to receive either acetaminophen ER 3900 mg/day or placebo. Subjects were instructed to call the interactive voice response system (IVRS) between 1:30 and 3:30 PM (and at least one hour after they completed the marathon) and to refrain from using any analgesics until after calling the IVRS. Subjects who rated their muscle soreness at least four on a zero-to-ten point scale were instructed to start study medication. Subjects who provided a rating of three or less were not eligible to continue in the study. Subjects who qualified then called the IVRS to provide their evening assessment between 9:00 and 11:00, prior to taking their evening dose of medication.

During the three days after the marathon (Day 2 through Day 4), subjects called the IVRS each morning and each evening to answer certain questions concerning muscle soreness, sleep

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interference, daily activity, ability to go for a run, and satisfaction with treatment. During the evening call of Day 3, subjects also answered certain questions on disability from the ODI. Subjects received a phone call one to five days after the last dose of study medication. This call allowed for adverse events (AE), concomitant medications, and treatment compliance` to be recorded. Subjects who had inadequate pain relief and required rescue medication were withdrawn from the study.

Number of Subjects (planned and analyzed):
It was planned that 600 subjects would be randomized and experience a muscle aching and pain (soreness) of at least four on a zero-to-ten point scale.

A total of 788 subjects were screened; 665 were randomly assigned to treatment, 616 received study treatment and were included in the safety analysis, and 610 were included in the intent-to-treat analysis. The per-protocol analysis consisted of 593 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects were required to be 18 years of age or older, provide informed consent, be able to comply with the study visit schedule, and be able to swallow the study medication. Subjects must have completed the marathon and agreed not to take any analgesics after the marathon until they called the IVRS (between 1:30 and 3:30 PM and at least one hour after completing the marathon) when their eligibility was determined. At that time, subjects who rated their muscle soreness at least four on a zero-to-ten point scale were eligible to continue in the study.

Test product, dose and mode of administration, batch number: Study drug treatment was two 650-mg caplets three times a day of Acetaminophen ER. Batch number was HMM0001489.

Duration of treatment: Subjects were treated with multiple doses of study drug over a 4-day period.

Reference therapy, dose and mode of administration, batch number: Reference therapy was two inert caplets three times a day of placebo. Batch number was KG2001030.

Criteria for Evaluation:
Efficacy:
The protocol-specified primary efficacy endpoint was the average change from baseline in muscle soreness on Day 1 (the day of the marathon).
Secondary endpoints included the following:

- Average change from baseline in muscle soreness for both morning and evening assessments
- Average change from baseline in muscle soreness for morning assessments
- Average change from baseline in muscle soreness for evening assessments
- Average ratings of interference with sleep
- Average interference with daily activity
- Average interference with the ability to go for a run

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- Time it takes for subjects to report no interference with the ability to go for a run
- Oswestry Disability Index
- Overall satisfaction with treatment

Other endpoints of a priori interest were:

- Baseline muscle soreness in subjects who did not take an analgesic prior to the race and subjects who took an analgesic prior to the race. Those subjects who did take an analgesic prior to the race were further evaluated by if they had taken acetaminophen, ibuprofen or any form of naproxen.
- Proportion of subjects discontinuing due to lack of efficacy.
- Proportion of subjects with a sustained 50% reduction in pain intensity starting on Day 2, starting on Day 3, etc.
- Proportion of subjects who went for a run on Day 2, Day 3, etc, for all subjects, those who had run more than one marathon, and those who had run their first marathon.
- Average miles per day that subjects ran during the three days following the marathon, for all subjects, those who had run more than one marathon, and those who had run their first marathon.

Safety: Safety assessments consisted of monitoring adverse events at the final phone visit.

Statistical Methods:

The null hypothesis of the study was that there is no difference between the two treatment groups in the change from baseline to the evening of Day 1 in the post-race muscle aching and pain (soreness) score. The alternative hypothesis was that a significant difference in the change from baseline to evening of Day 1 does exist.

All primary and secondary analyses were performed using the ITT population. All primary and secondary variables were summarized by time point and overall for each treatment group separately and pooled over both arms. Only 2% of the ITT population had major deviations. An analysis of the primary efficacy endpoint was also performed using the per-protocol population.

The hypotheses were tested using an ANCOVA model including terms for treatment, whether a subject took an OTC analgesic prior to the marathon (yes/no), the interaction between whether a subject took an OTC analgesic prior to the marathon and treatment, and baseline muscle aching and pain (soreness) as the covariate. If the interaction term was not significant at the 0.1 level, it was dropped from the model, and a main effect model including treatment, baseline muscle aching and pain (soreness), and whether a subject took an OTC analgesic prior to the marathon was fitted. If the effect of whether a subject took a prior OTC analgesic was significantly different for each treatment group (ie, the interaction term was significant at the 0.1 level) then this was investigated further. For example, the difference in adjusted means for each treatment was examined for each value of whether a subject took an OTC analgesic prior to the marathon.

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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 two-sided t-test at the 0.05 alpha level.

Homogeneity of the continuous variables for demographic and baseline characteristics was assessed by t-test, and Fisher's exact test for categorical variables.

Safety was evaluated by encoding all verbatim adverse reactions to standard dictionary coding terms and tabulating the overall safety profiles as well as according to system organ class, intensity, and relatedness to study treatment. Adverse event rates were compared using Fisher's exact test.

Efficacy Results:
The acetaminophen ER group reported a significantly greater decrease in the primary endpoint of average change from baseline in muscle soreness on Day 1 (-0.79) than the placebo group (-0.36, p=0.0001).

Eight secondary endpoints were as follows: average change from baseline in muscle aching and pain (soreness) for both morning and evening assessments, for morning assessments, and for evening assessments; average interference with sleep; average interference with daily activity; average interference with the ability to go for a run; change from baseline to Day 3 in the Oswestry Disability Index; and overall satisfaction with treatment. Results for seven of the eight secondary endpoints directionally favored acetaminophen over placebo; however, there were statistically significant differences in favor of acetaminophen for two of the secondary endpoints, ie, average interference with sleep and overall satisfaction with treatment. The adjusted mean for the average interference with sleep was significantly lower for the acetaminophen ER group (2.14) than for the placebo group (2.52, p = 0.0046). The adjusted mean overall satisfaction with treatment was significantly higher for the acetaminophen ER group (5.38) than for the placebo group (4.64, p = 0.0060).

There were no statistically significant differences between treatment groups for the following additional secondary endpoints: time to no interference with the ability to go for a run, lack of efficacy, sustained reduction in pain intensity, went for a run on each of Days 2 through 4 following the marathon, and average number of miles run during three days following the marathon.

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Results for the primary and secondary efficacy endpoints are summarized below:

Endpoint	LS Means: Acetaminophen ER N=307	LS Means: Placebo N=303	Difference (Acetaminophen ER – Placebo)	p-Value[a]
Change from baseline to evening of Day 1[b]	-0.79	-0.36	-0.42	0.0001
Average change from baseline over 4 days in muscle aching and pain (soreness) for both morning and evening assessments[c]	-2.63	-2.50	-0.13	0.2095
Average change from baseline over 4 days in muscle aching and pain (soreness) for morning assessments[c]	-2.58	-2.50	-0.08	0.4916
Average change from baseline over 4 days in muscle aching and pain (soreness) for evening assessments[c]	-2.66	-2.50	-0.17	0.1028
Average interference with sleep[c]	2.14	2.52	-0.38	0.0046
Average interference with daily activity[c]	3.02	3.18	-0.15	0.2432
Average interference with the ability to go for a run[c]	5.43	5.64	-0.21	0.2306
Change from baseline to Day 3 in Oswestry Disability Index[d] (%)	14.22	15.02	-0.81	0.3888
Overall satisfaction with treatment[c]	5.38	4.64	0.73	0.0060

a: p-Value from two-sided t-test of difference in adjusted means (significance at 0.05 level)
b: Final ANCOVA model contained terms for treatment, baseline muscle aching or pain (soreness), whether a subject took an OTC analgesic prior to the marathon, and treatment by whether a subject took an OTC analgesic prior to the marathon.
c: Final ANCOVA model contained terms for treatment, baseline muscle aching and pain (soreness) and whether a subject took an OTC analgesic prior to the marathon
d: Final ANCOVA model contained terms for treatment, baseline Oswestry Disability Index (%) and whether a subject took an OTC analgesic prior to the marathon

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Safety Results: Both study medications were well tolerated and no safety issues were identified. The nature and severity of adverse events were similar for both treatment groups. Overall, 3.7% of subjects reported adverse events; there was no statistically significant difference between treatment groups. Individual adverse event terms were reported in no more than two subjects per treatment group. There were no statistically significant differences between treatment groups for any adverse event. Three subjects withdrew early from the study; there was no significant difference between treatment groups. No serious adverse events or deaths were reported.

Conclusions:

- Acetaminophen ER was statistically significantly superior to placebo in the treatment of post-race muscle aching and pain (soreness) on the day of the marathon, as demonstrated by the primary efficacy endpoint of average change from baseline in muscle soreness on Day 1.

- Acetaminophen ER was statistically significantly superior to placebo for two of the eight secondary endpoints, ie, interference with sleep and overall satisfaction with treatment. There were no statistically significant differences between the two treatments for the other six secondary endpoints.

- Acetaminophen ER and placebo were well tolerated and no safety issues were identified. There were no statistically significant differences between treatment groups in the incidence of adverse events. No serious adverse events or deaths were reported.

Date of the report: August 26, 2004