

1. SYNOPSIS

<p>Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals</p> <p>Name of Finished Product: Tylenol® Arthritis Pain Extended Relief Caplets</p> <p>Name of Active Ingredient: Acetaminophen ER</p>	<p>Individual Study Table Referring to Part of the Dossier</p> <p>Volume:</p> <p>Page:</p>	<p>(For National Authority Use Only)</p>
<p>Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study Evaluating Acetaminophen Extended Release (3900 mg/day) in the Treatment of Osteoarthritis of the Hip or Knee.</p> <p>Investigators: Multiple (60 investigators); see Section 4, Investigators and Study Administrative Structure.</p> <p>Study Centers: Multiple (58 centers in the United States); see Section 4, Investigators and Study Administrative Structure</p> <p>Publication (reference): None.</p> <p>Study Period: Phase of Development: III Date of first enrollment: January 15, 2004 Date of last completed: October 25, 2004</p> <p>Objectives: The study objective was to evaluate acetaminophen extended release (ER) (3900 mg/day) compared to placebo for safety and efficacy in the relief of signs and symptoms of osteoarthritis of the hip or knee over 12 weeks.</p> <p>Methodology: This was a phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled study of 542 subjects. Enrolled subjects were 40 years of age and older, experiencing moderate, moderately severe, or severe pain when not taking osteoarthritis analgesic medication secondary to osteoarthritis of the hip or knee. After obtaining informed consent, each subject's eligibility was assessed through a screening visit with the following measures:</p> <ul style="list-style-type: none"> • Physical examination including vital signs and weight, medical history review, study joint and physical disability assessments, laboratory evaluation, and radiographic assessment of the symptomatic hip or knee. • Assessment of study joint pain, physical function and stiffness using the visual analog scale (VAS) version of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. 		

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- History (ie, at any time in the past) of osteoarthritis pain of the hip or knee when not taking osteoarthritis analgesic medication. Level of pain was measured on a five point scale defined as none (0), mild (1), moderate (2), moderately severe (3), or severe (4). Subjects must have reported a history of a pain level of moderate (2), moderately severe (3), or severe (4).

Following the screening visit, all potential subjects underwent a washout period from their current osteoarthritis pain medication.

Subjects returned to the study center for a baseline visit when eligibility was verified by the following assessments:

- Screening laboratory test results were reviewed, a study joint assessment was conducted, and vital signs were recorded.
- The VAS version of the WOMAC Osteoarthritis Index was administered. Subjects had to demonstrate a pain subscale score ≥ 65 mm (based on a normalized 0 to 100 mm VAS scale) and an increase of $\geq 20\%$ relative to that determined at the screening visit in order to be eligible to be randomized.
- Maximum osteoarthritis pain intensity experienced over the 24 hours prior to the baseline visit was measured on a five point scale as defined as none (0), mild (1), moderate (2), moderately severe (3), or severe (4). Subjects must have reported a pain level of moderate (2), moderately severe (3), or severe (4).
- The Nottingham Health Profile (NHP) was administered.

After completing the baseline visit, eligible subjects were randomly assigned to receive acetaminophen ER (3900 mg/day) caplets or placebo. Subjects were to take their assigned study medication every eight hours for 12 weeks or until study discontinuation.

Subjects were permitted to use self-administered nonpharmacologic therapies for breakthrough osteoarthritis study joint pain to the extent that they were not newly initiated during the subject's participation in the study and did not require the supervision of a healthcare provider.

If pain relief was inadequate, rescue analgesic medication was permitted on a limited basis for study joint related pain, ie, no more than three days in any seven-day period. A

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<p>prescription for a predetermined quantity of propoxyphene hydrochloride (HCl) 65 mg capsules was supplied to the subjects at the baseline visit and at each follow-up visit. Subjects were permitted to take rescue analgesia up to a maximum recommended dose of two capsules, three times daily, for no more than three days in any seven-day period. Subjects were not permitted to use any nonpharmacologic therapies that required the direct supervision of a healthcare provider (eg, physical therapy, etc) within 48 hours prior to returning to the study center for follow-up. Subjects were not permitted to use additional analgesic medication, including rescue analgesia, within five (ie, ≤ five) drug half-lives, plus an additional 48 hours, before returning to the study center for follow-up.</p> <p>Subjects returned for follow-up visits at the end of Weeks 2, 4, 8, and for a final visit at the end of Week 12 of treatment or upon early discontinuation from the study. The following assessments were performed at these visits:</p> <ul style="list-style-type: none"> • The VAS version of the WOMAC Osteoarthritis Index was administered. • Specimens were collected for laboratory evaluations and vital signs were recorded. • Subject's global assessment of response to therapy was obtained and the study joint was assessed. • The Nottingham Health Profile was administered. <p>Number of Subjects (planned and analyzed): The study was designed for the enrollment and randomization of approximately 520 subjects. Data were available for 542 subjects (267 subjects in the acetaminophen 3900 mg/d group and 275 in the placebo group); all of whom were included in an intent-to-treat (ITT) efficacy analysis and safety analysis.</p> <p>Diagnosis and Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> • Subjects of either sex, 40 years of age or older who had symptomatic idiopathic osteoarthritis of the hip or knee for a minimum of six months that required treatment with an analgesic (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen or other analgesic agents) or an anti-inflammatory agent on a regular basis (≥ three days/week) for at least three months before the screening visit. • Subjects had a history (ie, at any time in the past since diagnosis) of osteoarthritis of the hip or knee of at least moderate pain intensity when not taking osteoarthritis analgesic medication. • At the post-washout baseline visit, subjects demonstrated ≥ 65 mm (based on a normalized 0 to 100 mm VAS scale) on the WOMAC pain subscale score and an increase of ≥ 20% relative to that determined at the screening visit. 		

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<ul style="list-style-type: none"> • Subjects must have demonstrated radiographic evidence of mild to moderate osteoarthritis based on the Kellgren and Lawrence radiographic entry criteria of grade 2 or 3. • Subjects were American College of Rheumatology (ACR) Functional Class I, II, or III. • At the post washout baseline visit, subjects reported a maximum pain intensity experienced over the previous 24 hours of 2, 3, or 4 on a five-point scale of none (0), mild (1), moderate (2), moderately severe (3), or severe (4). <p>Test Product, Dose and Mode of Administration, Batch Number: Study medication treatment was two 650-mg caplets of acetaminophen ER taken orally three times/day (tid) [total dose 3900 mg/day], Batch number was HMM0001489.</p> <p>Duration of Treatment: Subjects were treated with multiple doses of study medications over a 12-week period.</p> <p>Reference Therapy, Dose and Mode of Administration, Batch Number: The reference therapy was two placebo caplets taken orally tid, Batch number was KG2001030.</p> <p>Criteria for Evaluation:</p> <p>Efficacy: The primary efficacy endpoints were:</p> <ul style="list-style-type: none"> • The average change from baseline through Week 12 (or through the final on-therapy visit) for WOMAC pain subscale score. • The average change from baseline through Week 12 (or through the final on-therapy visit) for WOMAC physical function subscale score. • The subject's average global assessment of response to therapy through Week 12 (or through the final on-therapy visit). <p>The secondary efficacy endpoints were:</p> <ul style="list-style-type: none"> • The average change from baseline through Week 12 (or through the final on-therapy visit) for WOMAC stiffness subscale score. • The average change from baseline through Week 12 (or through the final on-therapy visit) for total WOMAC Osteoarthritis Index. • The average change from baseline through Week 12 (or through final on-therapy visit) for the Nottingham Health Profile (NHP) Energy subscale score. 		

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<p>Safety: Safety assessments consisted of monitoring vital signs, adverse events, study joint assessments, and clinical laboratory determinations at study visits.</p> <p>Statistical Methods: The analysis of primary efficacy endpoints was based on the ITT approach. All randomized subjects were included in the ITT population; whereas those subjects who had taken at least one dose of study medication were included in the safety analysis. An analysis of primary efficacy endpoints in the per-protocol (PP) population was also to be considered if there were protocol deviations in more than 10% of the ITT population.</p> <p>Demographic and baseline characteristics were summarized by treatment group using descriptive statistics. Comparability between groups was analyzed using either parametric or categorical methods depending on the scale of the measurement.</p> <p>The average change from baseline through Week 12 (or through the final on-therapy visit) in WOMAC pain subscale, physical function subscale, stiffness subscale, total WOMAC Index, and NHP Energy subscale was analyzed using analysis of covariance (ANCOVA) models with treatment and investigator as fixed effects and the corresponding baseline value as a covariate. The treatment-by-investigator interaction term was also evaluated. If the p-value for the interaction term was greater than 0.10, the interaction term was not included in the final model. Statistical comparisons of the active treatment group with placebo were made with respect to least-squares means.</p> <p>The subject's average global assessment of response to therapy through Week 12 (or through the final on-therapy visit) was analyzed using an ANCOVA model with treatment and investigator as fixed effects and the WOMAC pain subscale score at baseline as a covariate. Subjects without any subject assessment data were assigned an average global score of zero (none).</p> <p>Both the proportion of subjects discontinuing the study due to lack of efficacy and the proportion of subjects who were efficacy failures were analyzed using Fisher's exact test. Compliance to the dosing requirements of the study medication was summarized using descriptive statistics.</p>		

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The frequency of adverse events (AEs), serious AEs, and AEs leading to withdrawal from the study were compared between treatment groups with Fisher's exact test. An ANCOVA with treatment as a fixed effect and the corresponding baseline value as a covariate was used to test for differences in treatment group with respect to change from baseline during the study at various time points for vital signs.

The clinical laboratory tests were summarized. The following rates within each treatment were calculated.

1. Post-baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST) and either ALT or AST measurements >3x the upper limit of normal (ULN), >2x ULN to ≤3x ULN, and >1x ULN to ≤2x ULN.
2. Post-baseline total bilirubin measurements >1.5x ULN and >1x ULN to <2x ULN.
3. Post-baseline ALP measurements >1.5x ULN and >1x ULN to ≤ 1.5x ULN.
4. Post-baseline creatinine measurements >1x ULN to ≤2x ULN.

Efficacy Results: Overall, the mean age of the ITT study population was 61.7 years. The ITT study population was predominantly female (74.4%) and Caucasian (81.9%). There was no statistically significant difference between the treatment groups in any of the demographic or baseline characteristics.

As shown in the table below, acetaminophen 3900 mg per day was superior to placebo for two of the three primary efficacy endpoints, as indicated by statistically significantly greater mean change from baseline in the WOMAC physical function subscale score (p = 0.011) and a greater mean average subject's global assessment of response to therapy (p = 0.010). Acetaminophen 3900 mg per day was superior to placebo for the third primary efficacy endpoint, as indicated by borderline statistically significantly greater mean change from baseline in the WOMAC pain subscale score (p = 0.054).

Acetaminophen 3900 mg per day was superior to placebo for two of the three secondary efficacy endpoints, as indicated by statistically significantly greater mean change from baseline in the WOMAC stiffness subscale score (p = 0.004) and in the WOMAC total index (p = 0.013). Acetaminophen 3900 mg per day was superior to placebo for the third secondary efficacy endpoint, as indicated by borderline statistically significantly greater mean change from baseline in the Nottingham Health Profile Energy subscale score (p = 0.057).

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Mean Primary and Secondary Endpoints – Intent-to-treat

Mean Change from Baseline	Acetaminophen	Placebo	p-Value
WOMAC pain subscale score	-29.96	-25.75	0.054
WOMAC physical function subscale score	-26.64	-21.29	0.011
Subject's average global assessment of response to therapy	2.00	1.72	0.010
WOMAC stiffness subscale score	-26.91	-20.73	0.004
Total WOMAC Osteoarthritis Index	-27.34	-22.16	0.013
Nottingham Health Profile (NHP) Energy subscale score	-20.20	-15.95	0.057

Safety Results: All study medications were well tolerated and no significant safety issues were identified. The intensity and nature of adverse events were similar for the acetaminophen and placebo groups. There were no deaths during the study or during the follow-up period. Overall, ten subjects had serious adverse events, eight in the acetaminophen group and two in the placebo group (p = 0.060). None of the serious adverse events were considered to be drug related. Overall, 55.4% of subjects in the acetaminophen group and 57.8% in the placebo group reported adverse events. There were no significant differences between treatment groups in the percentage of subjects with adverse events or who discontinued study participation due to adverse events. Drug-related adverse events were reported by 16.1% of subjects in the acetaminophen group and 14.2% of subjects in the placebo group; there was no significant difference between treatment groups.

The treatment groups were similar with respect to percentages of subjects with adverse events in each system organ class. The system organ classes most commonly reported were gastrointestinal, general and administrative site conditions, infections and infestations, musculoskeletal and connective tissue, and nervous system disorders. There was a statistically significant difference between treatment groups for gastrointestinal disorders (p<0.001), with a greater percentage of subjects with adverse events reported in the acetaminophen group. In addition, there was a statistically significant difference between treatment groups for injury, poisoning, and procedural complications (p = 0.032), with a greater percentage of subjects with adverse events reported in the placebo group.

Evaluation of laboratory changes in individual subjects identified eight subjects whose liver function test values (AST and/or ALT) exceeded three times the upper limit of normal. Seven subjects were in the acetaminophen group and one was in the placebo group.

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Three subjects had mitigating circumstances, which may explain the abnormal laboratory values. In two of the seven acetaminophen-treated subjects, there was a concomitant condition or disease that may have been associated with the elevations of liver function test values. Another of the seven acetaminophen-treated subjects had an abnormal liver function test (AST) at screening. In four of the seven acetaminophen-treated subjects, liver function test values returned to or toward normal while the subject remained on drug treatment; one of these subjects had a single isolated (ALT only) abnormal value.

Minor changes in liver function tests were evaluated. There were nine subjects (3.4%) in the acetaminophen 3900 mg per day group and one subject (0.4%) in the placebo-treated group with peak AST or ALT values >2x ULN but ≤3x ULN.

There were no clinically important differences between treatment groups with respect to vital signs or weight.

Conclusions:

- Acetaminophen 3900 mg per day was superior to placebo for two of the three primary efficacy endpoints, as indicated by statistically significantly greater mean change from baseline in the WOMAC physical function subscale score (p = 0.011) and a greater mean average subject's global assessment of response to therapy (p = 0.010).
- Acetaminophen 3900 mg per day was superior to placebo for the third primary efficacy endpoint, as indicated by borderline statistically significantly greater mean change from baseline in the WOMAC pain subscale score (p = 0.054).
- Acetaminophen 3900 mg per day was superior to placebo for two of the three secondary efficacy endpoints, as indicated by statistically significantly greater mean change from baseline in the WOMAC stiffness subscale score (p = 0.004) and in the WOMAC total index (p = 0.013).
- Acetaminophen 3900 mg per day was superior to placebo for the third secondary efficacy endpoint, as indicated by borderline statistically significantly greater mean change from baseline in the Nottingham Health Profile Energy subscale score (p = 0.057).

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<ul style="list-style-type: none">Acetaminophen 3900 mg per day and placebo were well tolerated and no significant safety issues were identified in this study. There were no statistically significant differences between treatment groups in the overall incidence of adverse events or in the incidence of adverse events resulting in discontinuation from the study. The nature and intensity of adverse events were similar for both treatment groups. <p>Date of the Report: July 12, 2005</p>		

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