1 SYNOPSIS

Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals ***Name of Finished Product:*** Tylenol® Arthritis Pain Extended Relief ***Name of Active Ingredient:*** Acetaminophen ER	***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 (1950 mg/day and 3900 mg/day) in the Treatment of Osteoarthritis of the Hip or Knee.

Investigators: Multicenter

Study Centers: A total of 47 sites participated in this study. For a list of sites, see Appendix 14.1.4

Publication (Reference): Altman RD, Schweinle JE, Zinsenheim JR, Temple AR. Three-month efficacy and safety of acetaminophen for osteoarthritis pain of the hip or knee. Presented at the 9th World Congress of the Osteoarthritis Research Society International. December 4, 2004. Chicago, IL.

Study Period: ***Phase of Development:*** III
(date of first enrollment) April 17, 2002
(date of last completed) March 27, 2003

Objective: The study objective was to determine the safety and efficacy of 650 mg and 1300 mg acetaminophen given three times a day as Tylenol® Arthritis Pain Extended Relief caplets for the relief of signs and symptoms of osteoarthritis of the hip or knee for a period of 12 weeks.

Methodology: This was a phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled study of subjects who experienced at least moderate pain when not taking analgesic medication secondary to osteoarthritis (OA) pain of the hip or knee. After obtaining informed consent, each subject's potential eligibility was assessed through a screening visit. Following the screening visit, all potential subjects underwent a washout period from their usual OA pain medication. Subjects returned to the study center for a baseline visit to verify eligibility and to undergo study evaluations, including review of screening laboratory test results, study joint assessments, and vital signs recording. The visual analog scale (VAS) version of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index was administered. To be randomized, subjects must have

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demonstrated an increase in the pain subscale score of at least 20% (ie, ≥ 20%) relative to that determined at the screening visit, as well as have moderate or moderately severe OA pain intensity over the 24 hours prior to the baseline visit.

After completing the baseline visit, eligible subjects were randomly assigned to receive acetaminophen extended release (1950 mg/day), acetaminophen extended release (3900 mg/day) or placebo. The assigned study medication was taken every eight hours for 12 weeks or until study discontinuation.

Subjects were encouraged to use self-administered nonpharmacologic therapies (ie, therapies not under the direct supervision or administration by a health care provider) for breakthrough OA study joint pain during the study. For inadequate pain relief, rescue analgesic medication (propoxyphene HCl 65 mg) was provided and permitted on a limited basis (ie, for no more than three days in any seven-day period) for study joint related pain. Subjects were not permitted to use any unapproved nonpharmacologic therapies or additional analgesic medication, including rescue analgesia, within five (ie, ≤ 5) drug half-lives before returning to the study center for follow-up.

Subjects returned for follow-up visits at the end of Weeks 2, 4, 8, and 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: VAS version of the WOMAC Index, laboratory evaluations, vital signs recording, subject's global assessment of response to therapy, and study joint assessments.

Number of Subjects (Planned and Analyzed): 465 planned, 483 analyzed (160 in the acetaminophen 3900 mg/day group, 158 in the acetaminophen 1950 mg/day group, and 165 in the placebo group).

Diagnosis and Main Criteria for Inclusion: Subjects of either sex, 40 years of age or older, must have had symptomatic idiopathic OA of the hip or knee for a minimum of six months that required treatment with an analgesic [nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or other analgesic agents] or anti-inflammatory agent on a regular basis (≥ three days/week) for at least three months. Subjects must have had a history (ie, at any time in the past) of OA of the hip or knee of at least moderate pain intensity when not taking OA analgesic medication. Subjects must have demonstrated an

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increase in the WOMAC pain subscale score at baseline of at least 20% relative to that determined at the screening visit. 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 OA. Subjects must have been Functional Class I, II, or III. At the post washout baseline visit, subjects must have reported a maximum pain intensity experienced over the previous 24 hours of moderate (2) or moderately severe (3) on a five-point scale of none (0), mild (1), moderate (2), moderately severe (3), or severe (4).

Test Product, Dose and Mode of Administration, Batch Number:
Study drug treatment was Acetaminophen Extended Release: Caplets 650 mg x 1 tid, oral, Batch number KG2001044 and Acetaminophen Extended Release: Caplets 650 mg x 2 tid, oral, Batch number KG2001044.

Duration of Treatment:
Subjects were treated with multiple doses over a 12-week period.

Reference Therapy, Dose and Mode of Administration, Batch Number:
The reference therapy was Placebo: Inert Caplets, oral, Batch number EEM0001577.

Criteria for Evaluation:
Efficacy: The primary efficacy endpoints were:

- the average change from baseline through Week 12 (or final on-therapy visit) for WOMAC pain subscale score;
- the average change from baseline through Week 12 (or final on-therapy visit) for WOMAC physical function subscale score;
- the average subject's global assessment of response to therapy through Week 12 (or final on-therapy visit).

The secondary efficacy endpoints were:

- the average change from baseline through Week 12 (or final on-therapy visit) for WOMAC stiffness subscale score and the total WOMAC Index.
- the average number of rescue medication capsules taken per day while in the study (total number of rescue medication capsules taken divided by the total number of days in study).

Safety: Safety assessments consisted of monitoring vital signs, adverse events, study joint assessments, and clinical laboratory determinations at study visits.

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Statistical Methods: The hypothesis tested was that 1950 mg/day and/or 3900 mg/day acetaminophen extended release are superior to placebo in the treatment of osteoarthritis of the hip or knee with respect to all three primary efficacy endpoints. Statistical tests used a 0.05 significance level and were two-sided.

The analysis of efficacy (primary and secondary) was based on the intent-to-treat (ITT) population. All randomized subjects were included in the ITT population; however, data from specific visits could be excluded according to criteria specified in the Statistical Analysis Plan. An analysis of primary efficacy endpoints in the per-protocol (PP) approach was also performed by excluding those visits identified in the ITT analysis above and those thought to be contaminated by the use of concomitant medications or lack of study drug compliance within specified time periods; in addition, the PP analysis excluded all data for those subjects violating the inclusion/exclusion criteria specified in the Statistical Analysis Plan. The safety analysis was conducted on all randomized subjects who took at least one dose of study medication; in this study, the ITT and safety populations were identical.

The average change from baseline through Week 12 (or final on-therapy visit) in WOMAC pain subscale and physical function subscale was analyzed using analysis of covariance (ANCOVA) models with treatment and investigator as fixed effects and the corresponding baseline value as a covariate. Statistical comparisons of the two active treatment groups with placebo were made with respect to least-squares means for all three primary endpoints. No statistical comparisons were made between the two active treatment groups. For the primary endpoints, study joint (knee or hip) was considered as a subgroup variable by introducing Joint as a fixed effect and the interaction term of Joint and Treatment in the model.

For secondary efficacy endpoints, the average change from baseline for WOMAC stiffness subscale and total WOMAC index was analyzed with the same methods used for the primary efficacy variables. The mean number of rescue medication capsules taken per day was analyzed using an analysis of variance (ANOVA) model with treatment and investigator as fixed effects.

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The proportion of subjects discontinuing the study due to lack of efficacy and the proportion of subjects using more than the allowed amount of rescue medication were analyzed using Fisher's exact test. Additionally, the number of efficacy failures (defined as subjects discontinuing the study due to lack of efficacy or exceeding the recommended amount of rescue medication) was tabulated and analyzed using Fisher's exact test.

For the safety analysis, Fisher's exact test was used for treatment comparisons for adverse events and concomitant medication use. Vital signs and laboratory values were summarized by treatment group. Changes from screening in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, and total bilirubin were summarized by treatment group, as were the number of subjects with values outside the limits of normal and those that had values greater than two and greater than three times the limits of normal.

Other analyses included demographic and baseline characteristics (chi-square tests for categorical variables and one-way ANOVA for continuous variables), drug exposure and compliance (descriptive statistics), and reasons for withdrawal (descriptive statistics, with lack of efficacy withdrawals analyzed separately as described above).

Efficacy Results: Acetaminophen 3900 mg per day was superior to placebo with respect to all three primary endpoints, as indicated by statistically significantly greater mean change from baseline in WOMAC pain score (p=0.0120) and in WOMAC physical function score (p=0.0157), and a greater mean average subject's assessment of response to therapy (p=0.0153). It is important to note that the interaction term of drug and baseline pain was significant when the response was change from baseline in WOMAC pain, indicating that acetaminophen 3900 mg/day is superior to placebo with respect to pain at certain (high) values of baseline pain.

Acetaminophen 1950 mg/day was superior to placebo with respect to one primary endpoint (subject's assessment of response to therapy), as indicated by a statistically significantly greater mean score (p=0.0236).

Acetaminophen 3900 mg/day was superior to placebo with respect to one of the three secondary efficacy endpoints (WOMAC total index) (p=0.0151).

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The results of the ANCOVA on the primary efficacy variables showed that when Study Joint and the interaction term of Drug and Study Joint were introduced into the statistical models, the significance level of the interaction term was greater than 0.10, indicating that the treatment does not behave differently depending on the study joint (knee or hip).

Safety Results:
All study medications were well tolerated, and no significant safety issues were identified. In this study, the severity and nature of adverse events were similar among treatment groups. Overall, 44.4% of subjects in the acetaminophen 3900 mg/day group, 44.9% of subjects in the acetaminophen 1950 mg/day group, and 40.0% of subjects in the placebo group reported adverse events. There were no significant differences among treatment groups in percentage of subjects with adverse events, or who discontinued study participation because of adverse events.

There was one death in the study (a placebo subject) due to a car accident. The death was not considered to be related to the study drug. Overall, eight subjects had serious adverse events (three each in the acetaminophen 3900 mg per day and 1950 mg per day groups and two in the placebo group). None of the serious adverse events were considered to be drug related.

Drug-related adverse events were reported by 8.1% of subjects in the acetaminophen 3900 mg/day group, 9.5% of subjects in the acetaminophen 1950 mg/day group, and 4.8% of subjects in the placebo group; there was no statistically significant difference among treatment groups.

The body systems in which adverse events were most commonly reported were the body as a whole and the digestive system. The most commonly reported adverse events (reported by 20 or more subjects overall) were pain, infection, headache, and diarrhea; there were no statistically significant differences among treatment groups for these events.

There was a difference among treatment groups in the COSTART adverse event term of “liver function tests abnormal,” 3.1% (n = 5) of subjects in the acetaminophen 3900 mg per day group compared with 0% in both the acetaminophen 1950 mg per day group and the placebo group (p=0.0074). This event was considered to have a “possible” relationship to study drug in one subject, an unlikely relationship in one subject, and was “not related” in

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the other three subjects. Five additional acetaminophen-treated subjects (two on 3900 mg per day and three on 1950 mg per day) had related COSTART adverse event terms ("SGPT increased" with or without "SGOT increased") reported. In nine of ten subjects, all liver enzymes were reported as normal while the subjects continued on acetaminophen study treatment or after additional follow-up; in one subject, ALT (SGPT) and AST (SGOT) were at near-normal levels while the subject continued on acetaminophen treatment and after treatment was discontinued. Seven of the ten subjects with ALT and/or AST evaluations reported as adverse events had peak elevations of ≤2X ULN, none had elevations >2X ULN but ≤3X ULN, and three had elevations >3X ULN. An evaluation of liver enzyme elevations based on adverse event data provides limited useful information due to the variability inherent in adverse event reporting and in coding of adverse events. A direct evaluation of laboratory data provides a more complete evaluation.

The evaluation of laboratory changes in individual subjects identified three subjects whose liver function test values (AST and/or ALT) exceeded the potentially clinically important threshold of three times the upper limit of normal. All three subjects were in the acetaminophen 3900 mg per day group. In two subjects, there were concomitant diseases or medications being used that are associated with elevations in liver function tests. In the other subject, liver function test elevations returned toward normal while the subject remained on drug treatment.

Minor changes in liver function tests were evaluated. There were three subjects (1.9%) in the acetaminophen 3900 mg per day group with peak ALT values >2X ULN but ≤3X ULN; liver function test values subsequently were reported as normal in two subjects during the period while they continued on acetaminophen treatment, and in the other subject after the end of acetaminophen treatment.

There were no clinically important mean changes over time for any laboratory parameter in any treatment group. There were negligible mean changes over time in the five selected laboratory parameters: ALP, ALT, AST, creatinine, and total bilirubin.

There were no clinically important changes in vital signs or weight in any treatment group.

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Conclusions:

- Acetaminophen 3900 mg/day was superior to placebo with respect to all three primary endpoints, as indicated by statistically significantly greater mean change from baseline in WOMAC pain score (p=0.0120) and in WOMAC physical function score (p=0.0157), and a greater mean average subject's assessment of response to therapy (p=0.0153).

- Acetaminophen 1950 mg/day was superior to placebo with respect to one primary endpoint (subject's assessment of response to therapy), as indicated by a statistically significantly greater mean score (p=0.0236).

- Acetaminophen 3900 mg/day was superior to placebo with respect to one of the three secondary efficacy endpoints (WOMAC total index) (p=0.0151).

- Treatment did not behave differently depending on the study joint (knee or hip).

- Acetaminophen 3900 mg/day, acetaminophen 1950 mg/day, and placebo were well tolerated, and no significant safety issues were identified in this study. There were no statistically significant differences among treatment groups in the overall incidence of adverse events, the incidence of serious adverse events, or the incidence of adverse events resulting in discontinuation from the study.

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