

# Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial of the Long-Term (6–12 Months) Safety of Acetaminophen in Adult Patients with Osteoarthritis

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## ABSTRACT

**Objective:** This study evaluated the safety of acetaminophen 4 g/d administered for up to 12 months to adult patients with osteoarthritis pain, using naproxen 750 mg/d as an active comparator.

**Methods:** This multicenter, multidose, single-dummy, randomized, double-blind, active-controlled, parallel-group study enrolled patients with mild to moderate osteoarthritis pain of the hip or knee. Patients received acetaminophen 4 g/d or naproxen 750 mg/d for 12 months (group 1) or 6 months (group 2). Patients in both groups had follow-up visits at months 1, 3, and 6 of treatment (or at the time of study withdrawal). Patients in group 1 also had follow-up visits at months 9 and 12 (or at the time of study withdrawal). Tolerability evaluations consisted of determinations of hepatic (aminotransferase activities) and renal (serum creatinine) function, adverse events, and physical examinations. Adverse events reported by the patient or observed by the investigator during clinical evaluation were recorded. In addition, patients were questioned at each visit regarding the occurrence of adverse events using a nonspecific question. Investigators rated the intensity of adverse events and their subjective assessment of the relationship to study medication while blinded to the treatment group. At all visits, patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), in visual analog scale format, to assess pain, stiffness, and physical function over the previous 2 weeks. The primary efficacy end point was the mean change from baseline in the WOMAC pain subscale score at 6 months. Data from the 6- and 12-month groups were combined for analysis.

**Results:** Of 581 randomized patients, the safety population included 571 patients who received  $\geq 1$  dose of study medication. The 571 patients had a mean (SD) age of 59.3 (8.6) years, 395 (69.2%) were female, and 480 (84.1%) were white. Of 290 patients randomized to receive acetaminophen, 134 completed 3 months of treatment, 96 completed 6 months, 60 completed 9 months, and 55 completed a full 12 months. The median dose adherence ranged from 95.5% to 98.6% during the trial. The completion and adherence patterns were similar for patients receiving naproxen. Of 291 patients randomized to receive naproxen, 151 completed 3 months, 124 completed 6 months, 85 completed 9 months, and 80 completed 12 months. The median dose adherence ranged from 96.4% to 98.4% during the trial. No patient in either treatment group experienced hepatic failure, hepatic dysfunction, aminotransferase levels  $\geq 2 \times$  the upper limit of the reference range, renal failure, or serum creatinine levels  $\geq 1.5 \times$  the upper limit of the reference range. No statistically significant differences were observed between the 2 treatment groups in the proportion of

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patients who reported  $\geq 1$  adverse event (206 [71.8%] acetaminophen, 209 [73.6%] naproxen) or in the proportion of patients who discontinued treatment because of adverse events (71 [24.7%] acetaminophen, 63 [22.2%] naproxen). Among adverse events considered to be drug related and reported by  $\geq 1\%$  of patients, constipation and peripheral edema were reported more frequently in the naproxen group than in the acetaminophen group (9.9% vs 3.1% [ $P < 0.002$ ] and 3.9% vs 1.0% [ $P < 0.033$ ], respectively). No adverse event reported in the acetaminophen group was considered both serious and related to study medication. One subject in the naproxen group had an event that was considered serious and related to study drug: gastrointestinal bleeding. No statistically significant differences were observed between the 2 treatment groups for the primary efficacy end point.

**Conclusion:** With physician supervision, acetaminophen was found to be generally well tolerated in these patients for the treatment of osteoarthritis pain of the hip or knee for periods of up to 12 months. (*Clin Ther.* 2006;28:222–235) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** acetaminophen, analgesics, non-narcotic, osteoarthritis, pain, tolerability.

## INTRODUCTION

Acetaminophen is one of the most commonly used medications in the United States.<sup>1</sup> Available without a prescription, it is used for short-term, symptomatic pain relief and fever reduction by 23% of adults in the United States in any given week.<sup>1</sup> The next most commonly used medications identified in the same survey were ibuprofen (17%) and aspirin (17%).<sup>1</sup> Guidelines for the medical management of osteoarthritis prescribe acetaminophen as one of the first-line analgesic treatments.<sup>2–5</sup> As a result, acetaminophen is one of the most frequently used medications for this indication. For example, nearly one fourth of community-based practicing rheumatologists in the United States stated that they always prescribed acetaminophen for the management of patients with osteoarthritis of the hip, whereas  $< 10\%$  always prescribed NSAIDs.<sup>6</sup> This results in repetitive use of acetaminophen, often on a daily basis, for extended periods of time.

Clinical trials evaluating the use of acetaminophen in osteoarthritis have demonstrated efficacy with a favorable tolerability profile using doses of 4 g/d for pe-

riods of 3 to 12 weeks.<sup>7–11</sup> However, longer trials are needed because patients may require treatment for several months or even years for persistent or recurrent osteoarthritis pain.

One study evaluating acetaminophen 2.6 g/d and naproxen 750 mg/d administered for up to 2 years to adult patients with osteoarthritis found no evidence of hepatic damage or renal insufficiency in acetaminophen-treated patients based on laboratory assessments (aminotransferase activities, bilirubin, alkaline phosphatase, and creatinine) and reported adverse events.<sup>12</sup> One naproxen-treated patient was withdrawn from the study because of presumed toxic hepatitis. Both treatment groups had relatively high dropout rates (acetaminophen, 69%; naproxen, 61%), characteristic of long-term trials.

A search of the published literature (using MEDLINE, 1966–2005, and restricted to the English language) for randomized controlled trials using the search term *acetaminophen* found few that evaluated repetitive doses of acetaminophen  $> 4$  g/d.<sup>13,14</sup> In a recent placebo-controlled pharmacokinetics trial involving 36 healthy volunteers, plasma acetaminophen concentrations did not accumulate after 3 days of repeated acetaminophen administration at 1, 1.5, and 2 g q6h (4, 6, and 8 g/d, respectively).<sup>15</sup> All aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values remained within normal limits during the study.

To date, we are unaware of published (using the same search strategy described above) or unpublished McNeil-sponsored randomized clinical trials evaluating the tolerability of acetaminophen at the maximum recommended dose of 4 g/d for  $> 12$  weeks. The aim of the present study was to evaluate the tolerability of acetaminophen 4 g/d administered for up to 12 months to adult patients with osteoarthritis pain, using naproxen 750 mg/d as an active comparator.

## METHODS

This was a multidose, single-dummy, randomized, double-blind, active-controlled, parallel-group study conducted at 47 centers in the United States between May 5, 2000, and June 6, 2003. All patients provided written informed consent. The study protocol was approved by local institutional review boards, and the trial was conducted in accordance with the ethical principles in the Declaration of Helsinki and its amendments through October 1996.<sup>16</sup>

## Patients

Patients aged 40 to 75 years with symptomatic osteoarthritis of the hip or knee for  $\geq 6$  months, and a history of pain of mild or moderate intensity on a 5-point scale of *none* (0), *mild* (1), *moderate* (2), *moderately severe* (3), or *severe* (4) at screening were eligible to participate in this study. To be eligible, patients had to require treatment with either an analgesic or anti-inflammatory agent for  $\geq 3$  d/wk for  $\geq 3$  months before enrollment. Patients with osteoarthritis of the knee had to fulfill  $\geq 2$  of the following 5 criteria based, in part, on the clinical criteria established by the American Rheumatism Association<sup>17</sup>: morning stiffness of  $< 30$  minutes' duration, crepitus, bony tenderness, bony enlargement, and no palpable warmth. Eligible patients also had recent (obtained  $\leq 6$  months before screening) radiographic evidence of grade 2 or 3 osteoarthritis of the knee or hip (osteophytes at the joint margin),<sup>6,17-19</sup> were either American College of Rheumatology (ACR) functional class I (complete functional capacity with ability to carry on all usual duties without handicaps) or II (functional capacity adequate to conduct normal activities despite handicap, discomfort, or limited mobility of  $\geq 1$  joint), and could walk  $\geq 100$  feet without an assistive device (ie, cane, crutches, or walker). Laboratory values had to be consistent with a diagnosis of osteoarthritis, including an erythrocyte sedimentation rate of  $< 40$  mm/h and a rheumatoid factor of  $< 40$  IU/mL.

Key exclusion criteria were a history of recent (previous 12 months) surgery (including arthroscopy) or major trauma to the study joint, active inflammation, more severe radiographic criteria, or other clinical or laboratory evidence of more serious joint disease. Patients who had secondary osteoarthritis of the study joint or pseudogout of any joint were excluded. Patients requiring other long-term treatment with drugs that might interfere with assessments (eg, aspirin [doses  $> 325$  mg/d]; anticoagulants; corticosteroids within 2 months; hyaluronan within 3 months; or non-stable doses of anticonvulsants, antidepressants, tranquilizers, hypolipidemic agents, glucosamine, and chondroitin sulfate) were also not eligible to participate. Other exclusion criteria were pregnancy; lactation; previous gastric surgery; allergy to aspirin, NSAIDs, or study medications; active illnesses that could interfere with the conduct of the study (eg, peptic ulcer disease, inflammatory bowel disease, or clinically important renal or hepatic disease, based on the investigator's

judgment of the patient's clinical history or baseline laboratory assessments); drug dependency; and abuse of drugs or alcohol ( $\geq 3$  drinks/d). Alcohol consumption was monitored during study participation, and moderate drinking (generally considered  $< 3$  drinks/d) was permitted.

## Study Design

Eligibility screening assessments included physical examination; study joint assessment; laboratory evaluation; physical disability assessment; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and physical function subscales in the visual analog scale format; and radiographic assessment of the symptomatic joint. An Alcohol Timeline Followback drinking assessment was completed to evaluate alcohol consumption.<sup>20</sup> Eligible patients were required to discontinue their current antiarthritis medication(s) for a washout period ranging from 3 to 11 days, depending on the medication half-life. Patients then returned to the study center for a baseline visit to review the results of screening laboratory procedures, as well as to repeat all aspects of the screening visit except radiographic assessments. At the baseline visit, patients who reported mild, moderate, or moderately severe pain intensity over the previous 24 hours and had a  $\geq 20\%$  increase in WOMAC pain subscale score (relative to screening) were enrolled in the study.

Enrolled patients were randomized to receive either acetaminophen 4 g/d (1 g every 4–6 hours) or naproxen 750 mg/d (375 mg BID) for 12 months (group 1) or for 6 months (group 2). Patients were assigned to 1 of the 2 treatment groups in blocks of 4 using a computer-generated randomization code. (The study was initially designed as a 12-month investigation, but with US Food and Drug Administration [FDA] consent, patients enrolled later were randomized only for a 6-month period.) Patients in both groups were instructed to take a dose of study medication according to the specified dosing schedule, and to record daily in the patient diary any doses and dates of study medication missed. On a weekly basis, patients were asked to record in the diary any symptoms of illness or discomfort, supplemental medications taken, or changes in the use of long-term medications. At each visit, patients were instructed to return all study medication blister cards and any unused study medication.

### Study Assessments

Patients in both groups had follow-up visits at months 1, 3, and 6 of treatment (or at study withdrawal). Patients in group 1 also had follow-up visits at months 9 and 12 (or at study withdrawal). Tolerability assessments consisted of determinations of hepatic and renal function, adverse events, and physical examinations. The laboratory parameters considered the primary tolerability variables of interest were AST, ALT, serum creatinine, and hemoglobin. Values considered to be significantly abnormal were as follows: AST or ALT values  $\geq 3 \times$  the upper limit of the reference range; serum creatinine levels  $\geq 1.5 \times$  the upper limit of the reference range; and a hemoglobin decrease of  $\geq 2$  g/dL from baseline. If AST or ALT were significantly elevated, other hepatic enzymes would then be measured. Laboratory analyses were performed at a central laboratory (PPD Development Clinical Laboratory, Austin, Texas) using a Synchron LX 20 analyzer (Beckman Coulter, Fullerton, California). The central laboratory established its reference ranges based on a local Texas population of self-reported healthy subjects (702 males and 403 females for AST, 776 males and 422 females for ALT).

Adverse events reported by the patient or observed by the investigator during clinical evaluation were recorded. In addition, patients were questioned at each visit regarding the occurrence of adverse events using a nonspecific question (eg, Have you experienced any unusual signs or symptoms since your last visit?). Investigators rated the intensity of adverse events (mild, moderate, or severe) and their subjective assessment of the relationship to study medication (not related, unlikely, possible, probable/likely, or certain) while blinded to the treatment group to reduce bias. Additionally, adverse events were defined as nonserious or serious, based on standard FDA criteria for reporting adverse events.

An estimation of the number of doses actually taken over the treatment period was calculated using dosing data obtained from patient diaries, returned study medication blister cards, and unused study medication. Adherence to the dosing regimen was calculated by comparing the number of doses actually taken to the number of doses that should have been taken (number of days  $\times$  the number of doses per day) over the same treatment period.

At all visits, patients completed the WOMAC Index (visual analog scale format) to assess pain, stiff-

ness, and physical function over the previous 2 weeks. The primary efficacy end point was the mean change from baseline in the WOMAC pain subscale score at 6 months.

### Statistical Analysis

With  $\sim 100$  completed patients per group, there would be  $\sim 95\%$  power to detect  $\geq 1$  adverse event if its true underlying event rate was 3.0%. With a sample size of 60 patients per group, there was  $\sim 95\%$  power of detecting  $\geq 1$  adverse event if its true underlying rate was 5.0%. Based on the attrition rate in this study, 300 patients per treatment group were planned to be enrolled to provide 100 patients per treatment group at 6 months and 60 patients per treatment group at 12 months. The safety population included all patients who received  $\geq 1$  dose of study medication. Data were compared between treatment groups using the  $\chi^2$  test or Fisher exact test for categorical variables and 1-way analysis of variance, with treatment as a factor, for continuous variables. An analysis of covariance, with treatment and investigator as factors and baseline score as a covariate, was used for effectiveness data.

## RESULTS

### Patient Disposition and Demographic Characteristics

A total of 581 patients were randomized (Figure 1). Within group 1 (12-month subset;  $n = 476$ ), 237 were randomized to receive acetaminophen and 239 were randomized to receive naproxen. Within group 2 (6-month subset;  $n = 105$ ), 53 patients were randomized to receive acetaminophen and 52 were randomized to receive naproxen.

Of the 581 randomized patients, 571 patients received  $\geq 1$  dose of study medication (acetaminophen:  $n = 287$ ; naproxen:  $n = 284$ ) and were analyzed as the safety population. Within group 1 (12-month subset;  $n = 469$ ), 236 patients received acetaminophen and 233 received naproxen. Within group 2 (6-month subset;  $n = 102$ ), 51 patients received acetaminophen and 51 received naproxen.

Table I summarizes the baseline demographic characteristics of the safety population. The mean (SD) age was 59.3 (8.6) years, 395 (69.2%) were female, and 480 (84.1%) were white. No statistically significant differences were observed between the 2 treatment groups except for a small difference in mean height (0.8-inch mean difference,  $P < 0.021$ ) that was not

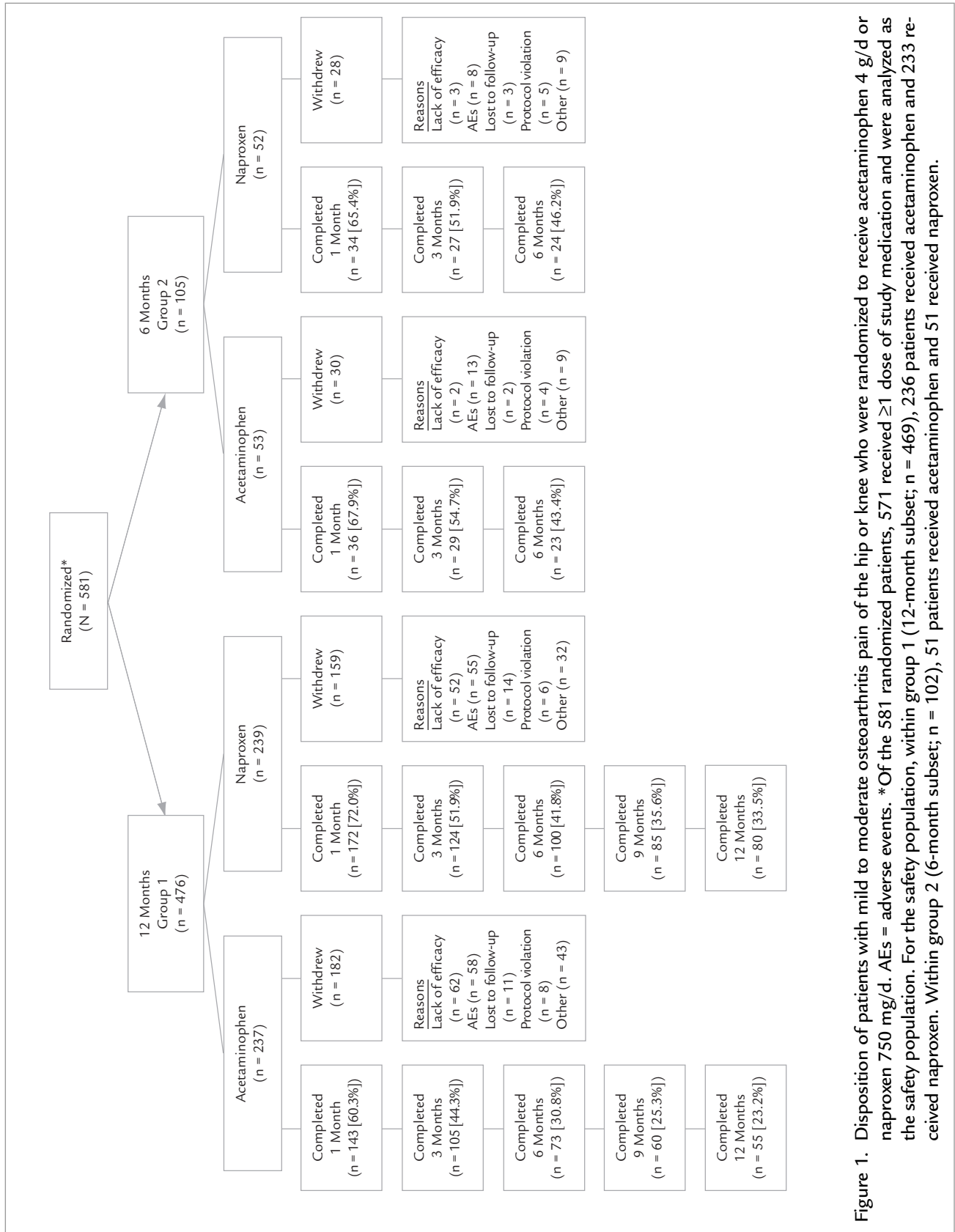


Figure 1. Disposition of patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized to receive acetaminophen 4 g/d or naproxen 750 mg/d. AEs = adverse events. \*Of the 581 randomized patients, 571 received  $\geq 1$  dose of study medication and were analyzed as the safety population. For the safety population, within group 1 (12-month subset; n = 469), 236 patients received acetaminophen and 233 received naproxen. Within group 2 (6-month subset; n = 102), 51 patients received acetaminophen and 51 received naproxen.

**Table I.** Baseline demographic characteristics for patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d or naproxen 750 mg/d.

Characteristic	Acetaminophen 4 g/d (n = 287)	Naproxen 750 mg/d (n = 284)	Total (N = 571)	P*
Age, y				<0.598
Mean (SD)	59.1 (8.9)	59.5 (8.3)	59.3 (8.6)	
Median	59.0	60.0	60.0	
Range	40.0–75.0	41.0–75.0	40.0–75.0	
Sex, no. (%)				<0.172
Female	191 (66.6)	204 (71.8)	395 (69.2)	
Male	96 (33.4)	80 (28.2)	176 (30.8)	
Race, no. (%)				<0.953 <sup>†</sup>
White	241 (84.0)	239 (84.2)	480 (84.1)	
Black	27 (9.4)	24 (8.5)	51 (8.9)	
Hispanic	17 (5.9)	21 (7.4)	38 (6.7)	
Other	2 (0.7)	0 (0.0)	2 (0.4)	
Height, in				<0.021
Mean (SD)	66.5 (3.8)	65.7 (4.1)	66.1 (4.0)	
Median	66.0	65.0	65.5	
Range	57.0–78.0	55.0–76.0	55.0–78.0	
Weight, lb				<0.230
Mean (SD)	204.8 (50.1)	200.0 (46.2)	202.4 (48.2)	
Median	197.0	193.1	195.0	
Range	92.0–420.0	112.0–350.0	92.0–420.0	

\*Based on the  $\chi^2$  test for categoric variables and 1-way analysis of variance, with treatment as a factor, for continuous variables.  
<sup>†</sup>Calculated using white and nonwhite categories.

considered clinically important. The mean (SD) weight was 202.4 (48.2) lb, with a range of 92.0 to 420.0 lb. Patients at the mean weight received an acetaminophen dose of 10.75 mg/kg, or 43 mg/kg daily. The patient with the lowest weight received acetaminophen at 23.8 mg/kg per dose, or 95.2 mg/kg daily; the patient with the highest weight received acetaminophen at 5.2 mg/kg per dose, or 20.8 mg/kg daily. These ranges reflect the real-world use of over-the-counter medications with fixed dosing schedules for all adults, regardless of height or weight. No analysis of efficacy versus dose was conducted.

#### Duration of Treatment and Dose Adherence

Of the 290 patients randomized to receive acetaminophen (groups 1 and 2), 179 (61.7%) completed 1 month, 134 (46.2%) completed 3 months, and 96 (33.1%) completed 6 months of treatment. Of the 237 patients randomized to receive 12 months of acetaminophen (group 1), 60 (25.3%) completed 9 months of treatment and 55 (23.2%) completed 12 months of treatment. Completion and discontinuation patterns were similar for the naproxen group.

The median dose adherence ranged from 95.5% to 98.6% during the period of the trial (Table II). The pattern of dosing adherence was similar for patients receiving naproxen. The mean monthly dose of acetaminophen for patients over the course of the trial was 100.9 g/month, with a maximum per protocol dose of ~120 g/month. For patients completing up to 6 months, the mean total dose of acetaminophen was 687.5 g; for those completing up to 12 months, the mean total dose was 1361.8 g.

The median dose adherence ranged from 95.5% to 98.6% during the period of the trial (Table II). The pattern of dosing adherence was similar for patients receiving naproxen. The mean monthly dose of acetaminophen for patients over the course of the trial was 100.9 g/month, with a maximum per protocol dose of ~120 g/month. For patients completing up to 6 months, the mean total dose of acetaminophen was 687.5 g; for those completing up to 12 months, the mean total dose was 1361.8 g.

#### Concomitant Medication and Alcohol Use

During the study period, 88.2% and 90.8% of patients in the acetaminophen and naproxen groups, respectively, received concomitant medications. No

Table II. Summary of adherence for patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d.

Time Interval*	No. of Patients	Adherence, % <sup>†</sup>			$\geq 66\%$ Adherence, No. (%) of Patients
		Mean (SD)	Median	Range	
Overall	278	83.0 (21.5)	93.1	3.6–100	229 (82.4)
Baseline to <month 1	278	86.2 (21.6)	95.5	2.1–100	241 (86.7)
Months 1 to <3	173	89.3 (19.4)	96.8	1.8–100	156 (90.2)
Months 3 to <6	127	91.9 (15.3)	98.1	22.9–100	117 (92.1)
Months 6 to <9 <sup>‡</sup>	71	92.8 (15.1)	98.6	14.0–100	66 (93.0)
Months 9 to 12 <sup>‡</sup>	60	91.4 (15.2)	98.0	20.3–99.7	57 (95.0)

\*From the day after the visit to the day of the next visit or study withdrawal.

<sup>†</sup>Percentage of adherence was calculated as  $100 \times ([\text{total number of doses taken}]/[\text{number of days in the study} \times 4])$ .

<sup>‡</sup>Includes patients in group 1 (12-month subset) only.

significant patterns of use could be established. At baseline, all patients in the acetaminophen group reported consuming a mean of <3 alcohol-containing drinks per day. During the treatment phase, 54.0% and 64.1% of patients in the acetaminophen and naproxen groups, respectively, reported consuming alcohol at some point during the study period. None of the patients in the acetaminophen group reported consuming  $\geq 3$  drinks/d during treatment.

### Hepatic Safety

There were no reports of hepatic failure or hepatic dysfunction. No patients had values  $>2\times$  the upper limit of the reference range (Table III). AST levels in 19 patients and ALT levels in 8 patients were reported to be  $>1\times$  the upper limit of the reference range. Scatterplots of AST and ALT absolute values over time in acetaminophen-treated patients are presented in Figure 2. For patients receiving acetaminophen, 97.6% (1361/1394) of the ALT and AST values were reported within the upper limit of the reference range throughout the study. Of the 54 total ALT or AST values above the upper limit of the reference range in both treatment groups, investigators recorded 7 as adverse events: 3 in the acetaminophen group and 4 in the naproxen group.

### Renal Safety

Table IV summarizes serum creatinine values for both treatment groups by assessment period. There

were no reports of renal failure. For the acetaminophen group, 98.1% (685/698) of serum creatinine values were reported below the upper limit of the reference range. No patient had serum creatinine levels  $\geq 1.5\times$  the upper limit of the reference range. Similar results were observed in naproxen-treated patients. Investigators reported 3 renal adverse events: 2 cases of mild renal insufficiency (acetaminophen,  $n = 1$ ; naproxen,  $n = 1$ ) and 1 case of nephritis (naproxen). The only renal adverse event considered probably/likely related to treatment (mild renal insufficiency) was in the naproxen group and resulted in discontinuation from the study. All renal adverse events resolved.

### Other Laboratory Data

Four patients in the acetaminophen group and 6 patients in the naproxen group had a decrease in hemoglobin levels of  $\geq 2$  g/dL. In the acetaminophen group, these decreases were below the reference range for 1 patient at month 6 (11.0 g/dL; reference range: 12.5–17.0 g/dL). No further follow-up was available for this patient. Two patients in the naproxen group had decreases in hemoglobin levels below the reference range; values for one of these patients returned to the reference range at follow-up visits.

### Adverse Events

Overall, 206 (71.8%) patients in the acetaminophen group and 209 (73.6%) patients in the naproxen

Table III. Summary of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values for patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d or naproxen 750 mg/d.

Treatment Group	Treatment Period											
	Month 1		Month 3		Month 6		Month 9		Month 12			
	AST	ALT	AST	ALT	AST	ALT	AST	ALT	AST	ALT	AST	ALT
Acetaminophen 4 g/d (n = 287)												
No. of values obtained	270	270	172	172	124	124	71	71	60	60		
Mean (SD), IU/L	25.3 (7.0)	23.4 (10.8)	24.8 (6.7)	23.2 (10.2)	23.9 (6.3)	22.9 (8.8)	22.3 (5.8)	22.1 (10.1)	25.1 (8.1)	24.5 (10.9)		
Relationship to reference range, no. (%) of values*												
Below	3 (1.1)	0	2 (1.2)	0	1 (0.8)	0	1 (1.4)	0	3 (5.0)	1 (1.7)		
Within	257 (95.2)	265 (98.1)	163 (94.8)	169 (98.3)	120 (96.8)	124 (100)	70 (98.6)	70 (98.6)	54 (90.0)	58 (96.7)		
Above	10 (3.7)	5 (1.9)	7 (4.1)	3 (1.7)	3 (2.4)	0	0	1 (1.4)	3 (5.0)	1 (1.7)		
Naproxen 750 mg/d (n = 284)												
No. of values obtained	269	268	193	193	148	148	98	98	85	85		
Mean (SD), IU/L	24.2 (7.3)	21.1 (12.8)	24.0 (7.6)	20.6 (9.3)	22.6 (5.9)	20.0 (8.8)	21.5 (4.7)	20.6 (9.3)	22.4 (5.3)	20.9 (8.8)		
Relationship to reference range, no. (%) of values*												
Below	1 (0.4)	0	1 (0.5)	0	3 (2.0)	0	2 (2.0)	0	2 (2.4)	0		
Within	261 (97.0)	265 (98.9)	188 (97.4)	191 (99.0)	143 (96.6)	146 (98.6)	96 (98.0)	97 (99.0)	83 (97.6)	85 (100)		
Above	7 (2.6)	3 (1.1)	4 (2.1)	2 (1.0)	2 (1.4)	2 (1.4)	0	1 (1.0)	0	0		

\*Reference ranges: AST, 11–44 IU/L; ALT, 0–60 IU/L.

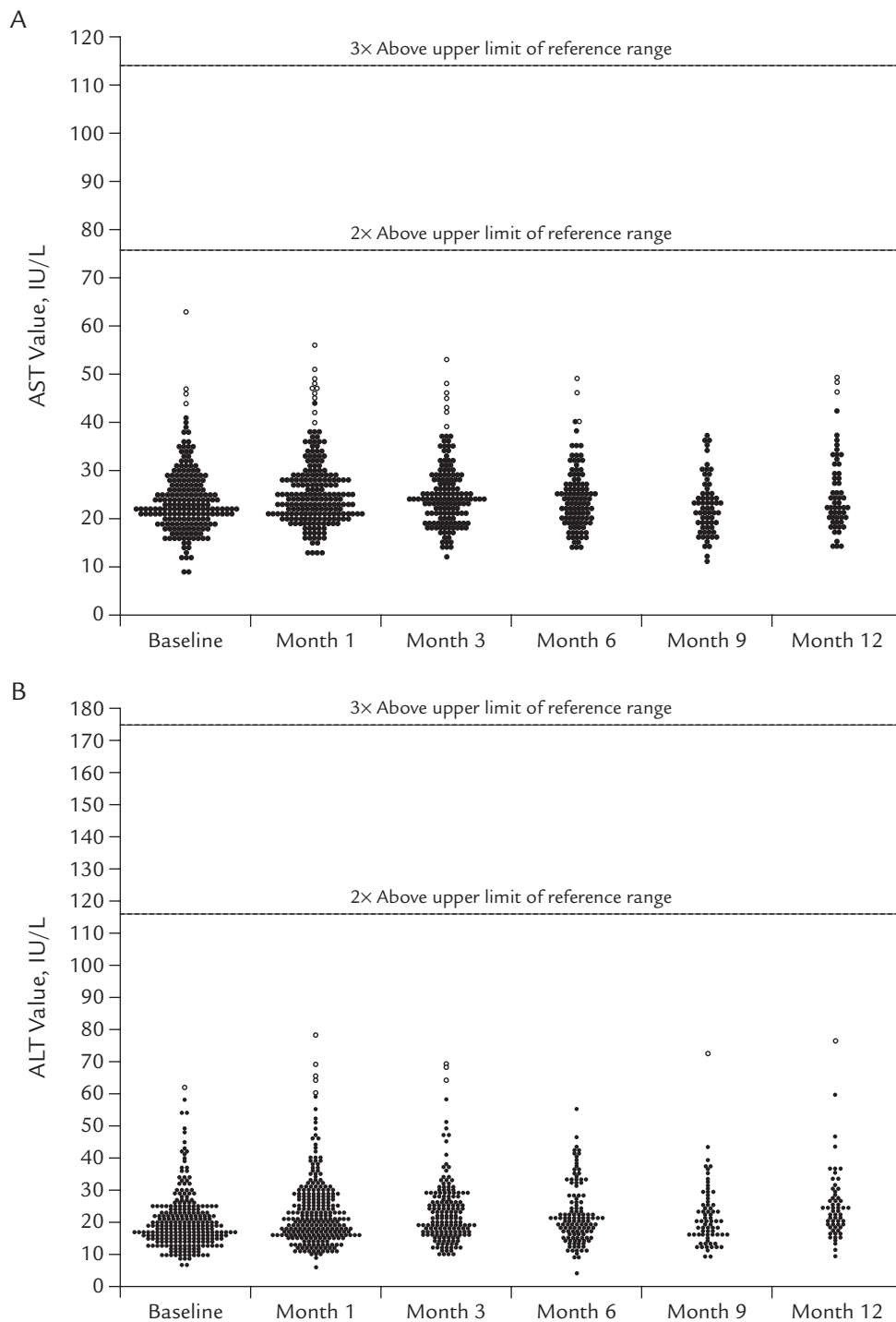


Figure 2. Scatterplots of hepatic function measurements over time in patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d. Empty circles indicate values  $>1\times$  to  $<2\times$  above the upper limit of the reference range. (A) Aspartate aminotransferase (AST) absolute values. (B) Alanine aminotransferase (ALT) absolute values.

Table IV. Summary of serum creatinine values for patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d or naproxen 750 mg/d.

Treatment Group	Treatment Period				
	Month 1	Month 3	Month 6	Month 9	Month 12
<b>Acetaminophen 4 g/d (n = 287)</b>					
No. of values obtained	271	172	124	71	60
Mean (SD), mg/dL	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.8 (0.2)	0.9 (0.2)
Relationship to reference range, no. (%) of values*					
Below	2 (0.7)	3 (1.7)	0	1 (1.4)	0
Within	263 (97.0)	166 (96.5)	122 (98.4)	69 (97.2)	59 (98.3)
Above	6 (2.2)	3 (1.7)	2 (1.6)	1 (1.4)	1 (1.7)
<b>Naproxen 750 mg/d (n = 284)</b>					
No. of values obtained	269	193	148	98	85
Mean (SD), mg/dL	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
Relationship to reference range, no. (%) of values*					
Below	1 (0.4)	4 (2.1)	2 (1.4)	0	0
Within	264 (98.1)	185 (95.9)	144 (97.3)	95 (96.9)	84 (98.8)
Above	4 (1.5)	4 (2.1)	2 (1.4)	3 (3.1)	1 (1.2)

\*Reference range: serum creatinine, 0.5–1.3 mg/dL.

group reported  $\geq 1$  adverse event ( $P = \text{NS}$ ). Table V lists drug-related adverse events that were reported in  $\geq 1\%$  of patients. Among these events, constipation and peripheral edema were reported more frequently in the naproxen group than in the acetaminophen group ( $P < 0.002$  and  $P < 0.033$ , respectively); no other statistically significant differences were observed.

Adverse events resulted in treatment withdrawal for 71 (24.7%) patients in the acetaminophen group and 63 (22.2%) patients in the naproxen group ( $P = \text{NS}$ ). The most common adverse events associated with early withdrawal were abdominal pain (4.2%), diarrhea (2.8%), nausea (2.4%), pain (2.1%), and dyspepsia (2.1%) in the acetaminophen group and abdominal pain (4.2%), pain (3.9%), dyspepsia (2.8%), and nausea (2.5%) in the naproxen group. There were no statistically significant differences between the 2 treatment groups for any adverse event leading to withdrawal.

Ten (3.5%) patients in the acetaminophen group (8 of whom withdrew) reported 12 serious adverse events, none of which was considered by investigators to be related to treatment. Seven (2.5%) patients in the naproxen group (3 of whom withdrew) reported 10 serious adverse events. One event of gastrointesti-

nal hemorrhage required study discontinuation. This was the only adverse event in either group considered to be both serious and related to study medication.

### Effectiveness

Acetaminophen and naproxen were similarly effective in relieving pain and stiffness and in improving physical function. In the acetaminophen group, mean changes from baseline to 6 months in the WOMAC pain (primary end point), stiffness, and physical function subscale scores were  $-21.6$ ,  $-20.6$ , and  $-18.9$ , respectively. No statistically significant differences were observed between the 2 treatment groups for the primary end point.

### DISCUSSION

To our knowledge, this is the first clinical trial to report results on the long-term use of acetaminophen 4 g/d for periods longer than 12 weeks<sup>7–11</sup> and at a dose higher than that used in another long-term-use trial, which evaluated a dose of 2.6 g/d for 2 years.<sup>12</sup> The results suggest that, in this study, the administration of acetaminophen 4 g/d for up to 12 months was well tolerated in the treatment of osteoarthritis of the hip or knee.

Table V. Drug-related adverse events reported in  $\geq 1\%$  of patients with mild to moderate osteoarthritis pain of the hip or knee who were randomized and received  $\geq 1$  dose of acetaminophen 4 g/d or naproxen 750 mg/d.\*

Adverse Event	Acetaminophen 4 g/d, No. (%) of Patients (n = 287)	Naproxen 750 mg/d, No. (%) of Patients (n = 284)	P†
Any adverse event	110 (38.3)	123 (43.3)	<0.235
Abdominal pain	29 (10.1)	18 (6.3)	<0.128
Dyspepsia	27 (9.4)	32 (11.3)	0.494
Diarrhea	20 (7.0)	10 (3.5)	0.090
Nausea	15 (5.2)	19 (6.7)	<0.485
Constipation	9 (3.1)	28 (9.9)	<0.002
Flatulence	9 (3.1)	8 (2.8)	1.000
Pruritus	8 (2.8)	3 (1.1)	<0.223
Headache	7 (2.4)	8 (2.8)	<0.801
Asthenia	5 (1.7)	4 (1.4)	1.000
Tinnitus	5 (1.7)	4 (1.4)	1.000
Eructation	4 (1.4)	3 (1.1)	1.000
Melena	4 (1.4)	4 (1.4)	1.000
Pain	4 (1.4)	11 (3.9)	<0.072
Rash	4 (1.4)	2 (0.7)	<0.686
Dry mouth	3 (1.0)	0	<0.249
Peripheral edema	3 (1.0)	11 (3.9)	<0.033
Somnolence	3 (1.0)	2 (0.7)	1.000
Dizziness	2 (0.7)	5 (1.8)	<0.284
Gastritis	1 (0.3)	3 (1.1)	<0.372
Insomnia	1 (0.3)	4 (1.4)	<0.215
Arthrosis	0	3 (1.1)	<0.123
Rectal hemorrhage	0	3 (1.1)	<0.123

\*Drug-related adverse events were those that were considered by the investigators to have a possible, probable/likely, or certain relationship to study medication administration.

†Based on the Fisher exact test.

The current study allowed a careful prospective look at dosing adherence patterns during prescribed long-term use of acetaminophen for the treatment of mild to moderately painful conditions. In this trial, patients who continued on acetaminophen therapy took >85% of their doses; more than half of these patients received >95% of their doses. This is a very high level of compliance, which may be related to the tolerability of the drug.

During the course of this trial, a small degree of variability in aminotransferase values was observed. In some cases, these values were  $>1 \times$  the upper limit of the reference range (AST levels in 19 patients, ALT levels in 8 patients). However, no patient had AST or ALT values  $>2 \times$  the upper limit of the reference

range, and values that were  $>1 \times$  the upper limit were often found to be within the reference range on subsequent assessment with continued drug treatment. This variability is not unlike that previously observed in patients who received placebo in trials.<sup>21-23</sup> Serum transaminase elevations have been observed in other clinical studies that have been conducted with acetaminophen.<sup>9,11,24,25</sup> However, only a small number of these elevations have been  $>3 \times$  the upper limit of the reference range (10 [1.3%] of 795 acetaminophen-treated patients).<sup>9,11,24,25</sup> The absence of increases in aminotransferase values  $>2 \times$  the upper limit of the reference range in this study suggests that long-term use of acetaminophen at recommended doses may not be associated with evidence of liver injury.

The present study is limited by the difficulties inherent in conducting long-term trials of subjects with osteoarthritis, for whom discontinuation rates may be high.<sup>12</sup> Thus, the number of subjects actually taking either medication for a full 12 months was limited. Because of this, the data on usage up to 6 months are more robust than the data for 12 months, and the data for use up to 3 months are even more robust. Another limitation is that the frequency of data assessments ranged from 1 to 3 months. Transient alterations in biochemical parameters that did not persist would not have been readily identified; however, the data gathered in this study suggest that if any such changes occurred, they did not persist. Because the upper age range limitation for the study was 75 years, these data may not be applicable to those aged >75 years. In addition, subjects were excluded if they had disease states that would have interfered with the assessments, were taking medications that might have confounded the efficacy analysis, had disease states that would have interfered with the use of naproxen, already had evidence of abnormalities of the primary safety end points, or were abusive users of drugs or alcohol. As such, the results were not determined in such patients with osteoarthritis.

## CONCLUSIONS

With physician supervision, acetaminophen was found to be generally well tolerated in these patients for the treatment of osteoarthritis pain of the knee or hip for periods of up to 12 months. Despite receiving at or near the maximum recommended daily dose for  $\geq 180$  days, no clinically important abnormalities in the results of AST, ALT, other liver function tests, or renal function were observed in these patients.

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