1 SYNOPSIS

Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals ***Name of Finished Product:*** ST. JOSEPH® ***Name of Active Ingredient:*** Aspirin, 81-mg chewable	***Individual Study Table Referring to Part of the Dossier*** Volume: Page:	(For National Authority Use Only)

Title of Study: Effect of Analgesics on the Irreversible Inactivation of Cyclooxygenase-1 Activity by Low Dose Aspirin and Endoscopic Evaluation of the Gastric Mucosal Effect

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Publication (reference): Bergeron A, Sun C, Wood J, et al. Effects of combining aspirin with non-steroidal anti-inflammatory drugs or COX-2 inhibitors on shear-induced platelet aggregation (abstract). Blood 2004; 104(11): 513a.

Sun C, Bergeron A, Wood J, et al. Effects of non-steroidal anti-inflammatory drugs and COX-2 inhibitors on aspirin-induced platelet inhibition (abstract). Blood 2004; 104(11): 154a.

Study period: ***Phase of Development:*** IV
Date of first enrollment: December 27, 2003
Date of last completed: March 28, 2004

Objectives: To examine in healthy volunteers the effects of analgesics given in approved daily doses in addition to daily cardio-protective doses of aspirin (81 mg) on: 1) cyclooxygenase (COX-1) activity in platelets as measured by platelet aggregation and thromboxane B_2, 2) cyclooxygenase activity in gastric mucosal biopsies, and 3) safety with respect to gastric toxicity as examined by endoscopy for erosions and ulcerations.

Methodology: This study was a randomized multiple-dose, single-blind, parallel-group study of 92 subjects conducted by a single investigator at one site in the United States. All site and laboratory personnel, except the person managing the medications, were blinded to the treatment group that subjects were assigned. All subjects were examined endoscopically before and after a course of study medication. All subjects received 81 mg aspirin daily for eight days and were randomly assigned to receive one of the following

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seven treatments administered concurrently on Days 1 through 8:

- Four doses of 1000 mg acetaminophen daily
- Three doses of 400 mg ibuprofen daily
- Two doses of naproxen daily (440 mg morning and 220 mg evening)
- No additional study medication
- Four doses of 650 mg aspirin daily
- Two doses of 200 mg celecoxib daily
- One dose of 25 mg rofecoxib daily

On Day 9 (Visit 6), each subject received an 81-mg aspirin dose 3½ to 4 hours before endoscopy was performed and a dose of the assigned study medication 1½ to 2 hours before endoscopy was performed (randomized study medication was to be administered 2 hours after the 81-mg aspirin dose was taken and 1½ to 2 hours before endoscopy was performed).

Two endoscopies were performed on each subject; the first was 2 weeks before starting study medication dosing (baseline endoscopy, Visit 2) and the second on Day 9 (Visit 6) after completing 8 full days of treatment and 1½ to 2 hours after taking the study medication on Day 9. The condition of the gastric mucosa was graded compositely according to the Lanza Mucosal Injury Scoring System and a visual recording was made of the entire endoscopy procedure. During the endoscopy, five gastric mucosal biopsy specimens were obtained, two from the gastric fundus and three from the gastric antrum (two biopsies for mucosal prostaglandin E_2 [PGE_2] and one for *Helicobacter pylori [H pylori])*. These biopsies were frozen in liquid nitrogen within 15 seconds of obtaining each one.

Blood was collected by venipuncture before the 81-mg aspirin dose and at four scheduled times (at 2-, 6-, 12- and 24-h) during the 24 hours after the 81-mg aspirin doses on Day 1 (Visit 3) and Day 8 (Visit 5) for platelet aggregation (arachidonic acid-induced), serum thromboxane B_2, and plasma PGE_2 testing. On Day 1, Day 2 and Day 8 blood was collected before the 81-mg aspirin dose to determine shear-induced platelet aggregation.

Subjects were given a diary in which to record the dates and times of study medication administration during the treatment phase. The subjects were contacted by telephone on Day 4 of the treatment phase to review study procedures, assess dosing compliance, inquire about adverse events and concomitant medications, and to remind them not to reveal to anyone in the endoscopy room the medications that they had been taking.

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Number of Subjects (planned and analyzed): The study was designed for the enrollment of at least 84 subjects. Data were available for all 92 randomized subjects, all of whom were included in the safety analysis. Efficacy analyses excluded 8 subjects.

Diagnosis and Main Criteria for Inclusion:

- 40-75 years of age
- normal hemostatic parameters
- healthy male and female subjects

Test product, dose and mode of administration, batch number: Lot numbers for all treatments were retained at the site. The seven treatment groups were as follows:

A. One ST. JOSEPH® Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and two TYLENOL® Extra Strength Caplets, 500 mg, administered by mouth 2, 6, 10, and 14 hours after the aspirin dosing. Doses were administered with 240 mL water.

B. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and two ADVIL® Caplets, 200 mg, administered by mouth 2, 8, and 14 hours after the aspirin dosing. Doses were administered with 240 mL water.

C. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and two ALEVE® Tablets, 220 mg, administered by mouth 2 hours after the aspirin dosing; and, one ALEVE Tablet, 220 mg, administered 14 hours after the aspirin dosing. Doses were administered with 240 mL water.

D. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole). Doses were administered with 240 mL water.

E. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and two Genuine Bayer® aspirin tablets, 325 mg, non-enteric coated, administered by mouth 2, 6, 10, and 14 hours after the aspirin dosing. Doses were administered with 240 mL water.

F. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and one CELEBREX® capsule, 200 mg, administered by mouth 2 and 14 hours after the aspirin dosing. Doses were administered with 240 mL water.

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G. One ST. JOSEPH Aspirin Tablet, 81 mg, non-enteric coated, chewable, administered by mouth (swallowed whole) and one VIOXX® tablet, 25 mg, administered by mouth 2 hours after the aspirin dosing. Doses were administered with 240 mL water.

Duration of treatment: Duration of participation in the study from screening to last endoscopy was approximately 44 days. Duration of treatment with the study medications was 8 full days (Days 1 through 8) of treatment and on Day 9, one dose of aspirin, 81 mg, and one dose of study medication.

Reference therapy, dose and mode of administration, batch number: Reference therapy was Treatment D consisting of 81-mg aspirin, chewable oral, only (Lot Number HJM173), with no additional analgesic administered.

Criteria for Evaluation:
Primary and Secondary Endpoints: Effects of analgesics on the inhibition of COX-1 activity by aspirin were evaluated by arachidonic acid-induced platelet aggregation in platelet-rich plasma, by measuring serum thromboxane B_2 levels using radioimmunoassay, and by testing shear-induced platelet aggregation. Injury to stomach mucosa was assessed by direct endoscopic observation of stomach mucosa and assigned a score based on the Lanza Mucosal Injury Score. Effects of analgesics on COX-1 activity in the stomach were evaluated by radioimmunoassay of gastric mucosal biopsy specimens obtained at endoscopy for PGE_2 concentrations. Inhibition of COX-2 systemically was evaluated by measuring plasma PGE_2 using radioimmunoassay.

Safety: Safety assessments consisted of routine monitoring for adverse events, as well as endoscopic examination of gastric mucosa for erosions and ulcerations occurring during the treatment phase.

Statistical Methods: Demographic and other baseline characteristic variables were summarized by treatment. Percent inhibition of percent arachidonic acid-induced platelet aggregation, serum thromboxane B_2 level, plasma PGE_2 and mucosal PGE_2 were analyzed using analysis of variance (ANOVA) with an arc sine transformation. The Lanza Mucosal Injury Scores were analyzed using a Cochran-Mantel-Haenszel test. Change from baseline of closure time for shear-induced platelet aggregation was analyzed using ANOVA. For all variables, pairwise comparisons were performed between aspirin 81 mg alone and all other treatment, and between aspirin 81 mg plus acetaminophen and all other treatments. All adverse events were summarized by body system and preferred term. Proportion of

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subjects reporting adverse events were analyzed using Fisher's Exact Test. Vital signs were analyzed using ANOVA.

Primary and Secondary Endpoint Results: Overall, the average age of the study population was 50.3 years and consisted of 55.4% female subjects and 78.3% Caucasians. Subjects who were randomized into one of seven treatment groups and who took at least one dose of study medication are included in the safety population. A per-protocol population was defined for each endpoint determination.

Primary Endpoints: Statistically significant effects for administration of 81-mg aspirin plus ibuprofen, naproxen or aspirin 2600 mg on arachidonic acid-induced platelet aggregation compared to both 81-mg aspirin alone and 81-mg aspirin plus acetaminophen were most frequently observed during the first 24 hours of treatment. At the end of the study, subjects taking 81-mg aspirin plus ibuprofen, celecoxib, 2600-mg aspirin, or naproxen had statistically significantly higher multiple-evaluator composite mucosal injury scores when compared to the 81-mg aspirin alone group. Subjects taking 81-mg aspirin plus naproxen or 2600-mg aspirin had statistically significantly higher multiple-evaluator composite mucosal injury scores when compared with subjects in the acetaminophen plus 81-mg aspirin group. Subjects in the acetaminophen plus 81-mg aspirin group had multiple-evaluator composite mucosal injury scores that were not statistically significantly different from the scores of subjects in the 81-mg aspirin alone group, $p= 0.085$; see Table 1.

On Day 1, there were statistically significant overall treatment effects on arachidonic acid-induced platelet aggregation observed at 6, 12, and 24 hours post dose ($p< 0.001$, $p< 0.001$, and $p= 0.009$, respectively). On Day 1, the groups receiving 81-mg aspirin plus ibuprofen, naproxen, or aspirin 2600 mg showed the greatest degree of inhibition of platelet aggregation, with maximum mean inhibition of 92.8% at 6 h, 93.7% at 24 h and 94.3% at 6 h, respectively (81-mg aspirin maximum mean inhibition was 60.8% at 24 h). On Day 8 (predose through 24 hours post dose), no statistically significant overall treatment differences were observed in inhibition of platelet aggregation among the treatment groups.

On Day 9, there was a statistically significant overall treatment effect on the multiple-evaluator composite Lanza Mucosal Injury Score ($p< 0.001$). The lowest mean Lanza multiple-evaluator Mucosal Injury Score was observed in the group receiving 81-mg aspirin alone (1.1). The highest scores were observed in groups receiving 81-mg aspirin plus naproxen (2.9) or 2600-mg aspirin (3.2).

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Table 1. Summary of Statistically Significant Results for Primary Endpoints

Variable	Time (Day, hours)	Significant vs Aspirin 81 mg [a]	Significant vs Aspirin 81 mg + Acetaminophen 4000 mg [b]
Percent Inhibition of Arachidonate-Induced Platelet Aggregation	Day 1 2 hours	-	-
	6 hours	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**
	12 hours	Acetaminophen 4000 mg **+** Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**	Rofecoxib 25 mg **—**
	24 hours	Naproxen 660 mg **+** Aspirin 2600 mg **+**	Rofecoxib 25 mg **—**
Percent Inhibition of Arachidonate-Induced Platelet Aggregation	Day 8 0 hours	Ibuprofen 1200 mg **—**	Ibuprofen 1200 mg **—**
	2 hours	Naproxen 660 mg **+**	-
	6 hours	-	-
	12 hours	Naproxen 660 mg **+** Celecoxib 400 mg **+**	-
	24 hours	-	-
Multiple-Evaluator Composite Mucosal Injury Score	Day 9	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+** Celecoxib 400 mg **+**	Naproxen 660 mg **+** Aspirin 2600 mg **+**

a: p≤0.050, p-value is for the pairwise comparison between this treatment and the 81 mg aspirin only group.
b: p≤0.050, p-value is for the pairwise comparison between this treatment and the acetaminophen plus 81 mg aspirin group.
+ = higher inhibition or higher mucosal injury score vs comparator; **—** = lower inhibition vs comparator

Secondary Endpoints: On Day 1, statistically significant ($p < 0.001$) overall treatment effects on inhibition of serum thromboxane B_2 were observed at 6, 12, and 24 hours post dose. On Day 1, groups receiving 81-mg aspirin plus ibuprofen, naproxen, or aspirin 2600 mg showed the greatest degree of inhibition of thromboxane B_2. On Day 8, small but statistically significant overall treatment effects on inhibition of serum thromboxane B_2 were observed at predose and at 2, 6, 12, and 24 hours post dose ($p \leq 0.028$); see Table 2.

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Table 2. Summary Statistically Significant Results for Secondary Endpoints: Thromboxane B_2

Variable	Time (Day, hours)		Significant vs Aspirin 81 mg[a]	Significant vs Aspirin 81 mg + Acetaminophen 4000 mg[b]
Inhibition of serum thromboxane B_2	Day 1	2 hours	Acetaminophen 4000 mg **—**	Naproxen 660 mg **+** Rofecoxib 25 mg**+**
		6 hours	Naproxen 660 mg **+** Aspirin 2600 mg **+**	Naproxen 660 mg **+** Aspirin 2600 mg **+**
		12 hours	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**
		24 hours	Naproxen 660 mg **+** Aspirin 2600 mg **+**	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+**
	Day 8	Predose	Ibuprofen 1200 mg **+** Aspirin 2600 mg **+** Celecoxib 400 mg **+** Rofecoxib 25 mg **+**	-
		2 hours	Ibuprofen 1200 mg **—**	Ibuprofen 1200 mg **—** Aspirin 2600 mg **+**
		6 hours	Aspirin 2600 mg **+** Rofecoxib 25 mg **+**	Aspirin 2600 mg **+** Rofecoxib 25 mg **+**
		12 hours	Aspirin 2600 mg **+**	Naproxen 660 mg **—** Aspirin 2600 mg **+**
		24 hours	Aspirin 2600 mg **+**	Naproxen 660 mg **+** Aspirin 2600 mg **+** Celecoxib 400 mg **+** Rofecoxib 25 mg **+**

a: p≤0.050, p-value is for the pairwise comparison between this treatment and the 81 mg aspirin only group.
b: p≤0.050, p-value is for the pairwise comparison between this treatment and the acetaminophen plus 81 mg aspirin.

+ = higher inhibition vs comparator; **—** = lower inhibition vs comparator

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No statistically significant overall treatment effects on percent inhibition of plasma PGE_2 were observed among treatment groups at any time point. On Day 9, statistically significant overall treatment effects on percent inhibition of gastric mucosal PGE_2 were observed. A statistically significantly ($p< 0.001$) greater degree of inhibition of gastric mucosal PGE_2 was observed in groups receiving ibuprofen plus 81-mg aspirin, naproxen plus 81-mg aspirin, 2600-mg aspirin plus 81-mg aspirin, celecoxib plus 81-mg aspirin, and rofecoxib plus 81-mg aspirin compared to groups receiving 81-mg aspirin or acetaminophen plus 81-mg aspirin, respectively; see Table 3.

Table 3. Results for Statistically Significant Secondary Endpoints: PGE_2

Variable	Time (Day)	Significant vs Aspirin 81 mg [a]	Significant vs Aspirin 81 mg + Acetaminophen 4000 mg [b]
Inhibition of plasma PGE_2	Day 1 Day 8	Not Statistically Significant at Any Time Period	
Inhibition of gastric mucosal PGE_2	Day 9	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+** Celecoxib 400 mg **+** Rofecoxib 25 mg **+**	Ibuprofen 1200 mg **+** Naproxen 660 mg **+** Aspirin 2600 mg **+** Celecoxib 400 mg **+** Rofecoxib 25 mg **+**

a: $p\leq0.05$, p-value is for the pairwise comparison between this treatment and the 81 mg aspirin only group.
b: $p\leq0.05$, p-value is for the pairwise comparison between this treatment and the acetaminophen plus 81 mg aspirin.

+ = Higher inhibition vs comparator; **—** = lower inhibition vs comparator

On Day 2, changes in closure times for shear-induced platelet aggregation in the presence of epinephrine were statistically significantly higher ($p< 0.001$) in groups receiving naproxen plus aspirin and 2600-mg aspirin plus 81-mg aspirin compared to groups receiving 81-mg aspirin alone or acetaminophen plus 81-mg aspirin. No statistically significant overall treatment effects or individual treatment group differences were observed in the change in closure time for shear-induced platelet aggregation in the presence of ADP at Day 2 or Day 8; see Table 4.

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Table 4. Results for Statistically Significant Secondary Endpoints: Shear-induced Platelet Aggregation

Variable	Time (Day, hours)	Significant vs Aspirin 81 mg [a]	Significant vs Aspirin 81 mg + Acetaminophen 4000 mg [b]
Inhibition of shear induced platelet aggregation (Epinephrine)	Day 2	Naproxen 660 mg **+** Aspirin 2600 mg **+**	Naproxen 660 mg **+** Aspirin 2600 mg **+**
	Day 8	**-**	**-**
Inhibition of shear induced platelet aggregation (ADP)	Day 2	Not Statistically Significant on Day 2 or Day 8	
	Day 8		

a: p≤0.05, p-value is for the pairwise comparison between this treatment and the 81 mg aspirin only group.
b: p≤0.05, p-value is for the pairwise comparison between this treatment and the acetaminophen plus 81 mg aspirin.

+ = Higher inhibition vs comparator; **—** = lower inhibition vs comparator

Safety Results: All study medications were well tolerated and no safety issues were identified. The severity and nature of adverse events were similar among treatment groups. Adverse events were reported by 16.3% of subjects; there were no statistically significant differences among treatment groups. The most commonly reported adverse events were gastrointestinal disorders (9.8%); there were no statistically significant differences among treatment groups. No subjects died or had other serious adverse events. No subjects discontinued study drug or were discontinued from the study due to adverse events.

Conclusions: On the basis of the results from the primary and secondary endpoints over the 9-day dosing period, when administered in addition to daily cardioprotective doses of aspirin (81 mg), the effects of analgesics given in approved daily doses were as follows:

- Aspirin 2600 mg, ibuprofen and naproxen treatments plus aspirin 81 mg, statistically significantly inhibited platelet aggregation more than an 81-mg aspirin dose alone in the first 24 hours of treatment. However, no clinically important interference or enhancement of 81-mg aspirin-mediated inhibition of platelet aggregation by these treatments was observed at the end of the study.

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- At the end of the study, subjects taking 81-mg aspirin plus ibuprofen, celecoxib, 2600-mg aspirin, or naproxen had statistically significantly higher multiple-evaluator composite mucosal injury scores when compared to the 81-mg aspirin alone group. Subjects taking 81-mg aspirin plus naproxen or 2600-mg aspirin had statistically significantly higher multiple-evaluator composite mucosal injury scores when compared with subjects in the acetaminophen plus 81-mg aspirin group. Subjects in the acetaminophen plus 81-mg aspirin group had multiple-evaluator composite mucosal injury scores that were not statistically significantly different from the scores of subjects in the 81-mg aspirin alone group, p= 0.085.

- Aspirin 2600 mg, ibuprofen and naproxen treatments plus aspirin 81 mg, statistically significantly inhibited serum thromboxane B_2 more than an 81-mg aspirin dose alone in the first 24 hours of treatment. Additionally, these analgesics had statistically significantly greater inhibition of serum thromboxane B_2 when compared to an 81-mg aspirin dose plus acetaminophen during the first 24 hours of treatment. No clinically important interference or enhancement of 81-mg aspirin-mediated inhibition of serum thromboxane B_2 by these treatments was observed at the end of the study.

- Aspirin 2600 mg, celecoxib, ibuprofen, naproxen and rofecoxib plus aspirin 81 mg, statistically significantly inhibited gastric mucosal prostaglandin E_2 more than either an 81-mg dose of aspirin alone or an 81-mg dose of aspirin plus acetaminophen at the end of the study.

- No interference or enhancement of 81-mg aspirin-mediated inhibition of shear-induced platelet aggregation was observed at the end of the study. However, during the first 24 hours of treatment there was a statistically significant prolongation of shear-induced closure time in the presence of epinephrine by naproxen and 2600-mg aspirin when compared to 81-mg aspirin alone or acetaminophen plus 81-mg aspirin.

- All study medications were well tolerated and no safety issues were identified. No subjects died, had other serious adverse events, or withdrew from the study because of an adverse event. There were no statistically significant differences among treatment groups in the incidence of adverse events.

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