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Link to drug label

Proprietary Drug Name	INN	Therapeutic area and FDA approved indications
Celebrex	Celecoxib	Relief of signs and symptoms of osteoarthritis Relief of signs and symptoms of rheumatoid arthritis in adults Management of acute pain in adults Treatment of primary dysmenorrhea Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care

Name of Sponsor/Company: Pfizer Pharmaceuticals Inc.

Title of Study: COXA-0508-253 (A3191074)
Final report for a double-blind, placebo-controlled, randomized two-week study, comparing small bowel lesions associated with celecoxib (200 mg bid) vs. naproxen (500 mg bid) plus omeprazole (20 mg qd)

Study centre(s): Nine (9) investigators enrolled subjects at 8 centers in the USA and 1 center in Israel.

Publication (reference, if applicable): See attached bibliography.

Studied period 26 Aug 2002 to 17 Apr 2003 | **Phase of development:** Phase 4

Objectives: The primary objective of this study was to assess the small bowel lesion pattern associated with celecoxib, 200 mg (BID) alone and with naproxen (500 mg BID) plus omeprazole (20 mg QD). The secondary objective was to assess the mucosal breaks, small bowel lesions and visible blood without visualized lesions in the small bowel associated with celecoxib alone and with naproxen plus omeprazole.

Methodology: This was a 4-week multicenter, double-blind, triple-dummy, placebo-controlled, active-comparator, randomized study, comparing small bowel lesions associated with celecoxib (200 mg BID) vs. naproxen (500 mg BID) plus omeprazole (20 mg QD) in healthy adult subjects. Eligible subjects received celecoxib (200 mg BID), naproxen (500 mg BID) and omeprazole (20 mg QD), or placebo to be taken orally for the duration of a 2-week treatment period.

This study consisted of 4 visits: Screening, Visit 2 (Day 14 ± 1), Visit 3 (Day 16 ± 1 / randomization) and Visit 4 (Day 30 ± 1 / final visit). The Screening visit marked the beginning of a 2-week (+/− 1 day) washout period necessary for a capsule endoscopic procedure. During this period the subject could not consume alcohol or use medication that could cause gastrointestinal mucosal lesions.

Study medication was dispensed at Visit 3, and all unused study medication was collected at Visit 4. Capsule endoscopic procedures were performed at Visits 2 and 4. Endoscopy capsules made by Given® Imaging Inc were used to provide an M2A Plus video of approximately 8 hours in duration. The endoscopy video was reviewed at the site. Videos from Visit 4 in which the site had noted at least 1 small bowel or gastric lesion were stripped of identifying information and comments from sites and then forwarded for review by a Small Bowel Events Committee (SBEC) for grading. The SBEC consisted of 4 gastroenterologists trained in interpretation of the M2A Plus data. All grades were assigned by complete consensus of the committee members. Subjects with small bowel mucosal breaks or visible blood at Visit 2 or if the small bowel video was less than 2 hours in duration were not eligible for randomization.

At Screening and Visit 3, subjects were given a Hemocheck fecal occult blood test kit, and those subjects

participating in the calprotectin portion of the study were given a calprotectin test kit. These test kits were collected with the fecal samples for analysis at Visits 2 and 4.

Telephone calls were made to each subject the day before Visits 2 and 4 to remind subjects to collect fecal occult blood test samples and to prepare for the capsule endoscopic procedure. A follow-up phone call was made 5 days after the capsule endoscopy to confirm capsule excretion. If capsule excretion could not be positively verified, an abdominal X-ray examination was required.

Number of patients (planned and analyzed): A total of 300 subjects were planned to be enrolled; Actual enrollment was 356 randomized to treatment (120 subjects in the celecoxib group, 118 subjects in the naproxen plus omeprazole group and 118 subjects in the placebo group). A total of 356 subjects were included in the safety population, 339 subjects were included in the modified intent-to-treat (MITT) population, and 312 subjects were included in the Evaluable population.

Diagnosis and main criteria for inclusion: Eligible subjects were healthy males or females 18 – 70 years of age with a normal, healthy gastrointestinal tract: ie, no small bowel mucosal breaks or blood found at Visit 2 based on the capsule endoscopic data review, history of gastrointestinal ulcers, bleeding or surgery, or complete or partial stenosis of the small intestine.

Duration of treatment: 2 Weeks

Test product, dose and mode of administration:

Celecoxib treatment: Subjects randomized to the celecoxib treatment group were treated with 200 mg celecoxib BID for 2 weeks. They took 1 capsule of celecoxib 200 mg, 1 placebo capsule identical to naproxen and 1 placebo capsule identical to omeprazole daily with the morning meal and 1 capsule of celecoxib 200 mg plus 1 placebo capsule identical to naproxen daily with the evening meal.

Reference therapy, dose and mode of administration:

Naproxen plus omeprazole treatment: Subjects randomized to the naproxen plus omeprazole treatment group were treated with 500 mg naproxen BID plus 20 mg omeprazole QD for 2 weeks. They took 1 capsule of naproxen 500 mg, 1 capsule of omeprazole 20 mg and 1 placebo capsule identical to celecoxib daily with the morning meal and 1 capsule of naproxen 500 mg plus 1 placebo capsule identical to celecoxib daily with the evening meal.

Placebo treatment: Subjects randomized to the placebo treatment group took 1 placebo capsule identical to naproxen, 1 placebo capsule identical to omeprazole and 1 placebo capsule identical to celecoxib daily with the morning meal and 1 placebo capsule identical to naproxen plus 1 placebo capsule identical to celecoxib daily with the evening meal.

Criteria for evaluation:

Efficacy: Clinical efficacy was not assessed in this study.

Safety: Videos of subjects with at least one lesion noted by the site were assessed by the SBEC. The findings of the SBEC constituted the lesion endpoints for these subjects. For the subjects whose videos showed no lesions at site review, the lesion count was zero. The primary endpoint was the number of mucosal breaks in the small bowel at the final visit as assessed by the SBEC and the sites on reviewing the endoscopy. Secondary endpoints were the percentage of subjects with at least 1 small bowel mucosal break, the total number of small bowel lesions with or without hemorrhage, and the percentage of subjects with visible blood in the small bowel without evidence of lesions. Exploratory endpoints were the number and incidence of gastric lesions and the results of the calprotectin and Hemocheck tests.

Statistical methods: The primary analysis population was the modified intent-to-treat population consisting of all randomized subjects who presented evaluable endoscopies at the Final visit. Incidence rates were compared between treatment groups using Cochran-Mantel-Haenszel statistics, stratified by site. The number of mucosal lesions of the various types was compared between treatment groups using Kruskal-Wallis and Wilcoxon Rank Sum statistics. The protocol-specified generalized linear model analysis of lesion counts was performed, but due to the non-normal distribution of the data, non-parametric methods were used instead.

Summary

Endoscopy results: The mean number of small bowel mucosal breaks at the Final visit was significantly higher in the naproxen plus omeprazole treatment group than in the celecoxib treatment group (0.32 for celecoxib group 2.99 for the naproxen plus omeprazole, and 0.11 for placebo group; p <0.001, MITT population). Similar observations were made in the analyses of gastric mucosal breaks and combined gastric or small bowel mucosal breaks. In the MITT population, celecoxib yielded significantly fewer mucosal breaks, gastric and small bowel, than the naproxen plus omeprazole combination. Fewer subjects in the celecoxib treatment group (16%) experienced small bowel mucosal breaks (grade 2,3,6,7) than subjects treated with naproxen plus omeprazole (55%) compared to 7% of the subjects treated with the placebo, and this difference was statistically significant. Gastric mucosal breaks were experienced by 3%, 38% and 6% of the celecoxib group, the naproxen plus omeprazole group, and the placebo group, respectively (p<0.001). The incidence rate for the subjects experiencing small bowel *or* gastric mucosal breaks was 17%, 65%, and 12% respectively, for the celecoxib group, the naproxen plus omeprazole group, and placebo group (p < 0.001). The results were similar in the Evaluable Population, and corresponding trends were noted in other endpoints as well. The most prevalent lesions were grade 2 (mucosal breaks without hemorrhage) bowel lesions and occurred less frequently in celecoxib or placebo group than in naproxen plus omeprazole group. The presence of blood without visualized lesions was found more rarely. The risk of this event was greater in the 2 active treatment groups than in the placebo group, but did not show statistically significant differences between the 2 active treatments.

Summary of Endoscopy Endpoints (MITT Population)

	Celecoxib N = 115	**Naproxen + Omeprazole** N = 111	**Placebo** N = 113	**p-value**
Number of subjects with small bowel mucosal breaks	18 (16%)	61 (55%)	8 (7%)	<0.001
Celecoxib vs placebo				0.040
Naproxen vs placebo				<0.001
Celecoxib vs naproxen				<0.001
Number of small bowel mucosal breaks				
Mean (SD)	0.32 (1.09)	2.99 (5.33)	0.11 (0.45)	<0.001
Range	0 – 9	0 – 30	0 – 3	
Celecoxib vs placebo				0.042
Naproxen vs placebo				<0.001
Celecoxib vs naproxen				<0.001
Number of subjects with blood without visualized lesions	8 (7%)	9 (8%)	1(1%)	0.034
Celecoxib vs placebo				0.014
Naproxen vs placebo				0.007
Celecoxib vs naproxen				0.754

Safety Results: The incidence of AEs and treatment-related AEs was similar among the treatment groups. The majority of AEs were mild or moderate in severity. The AEs in each treatment group were primarily in GI system disorders. The most commonly occurring AEs were abdominal pain, headache, diarrhea, nausea, dyspepsia, and flatulence. Of these, only headache, abdominal pain and flatulence occurred in more than 5% of the subjects in any 1 treatment group: Headache was reported by 3.3%, 1.7% and 8.5% subjects, respectively, in the celecoxib, naproxen plus omeprazole, and placebo groups. Abdominal pain was reported by 4.2%, 7.6% and 3.4%, respectively, in the celecoxib, naproxen plus omeprazole, and placebo groups. Flatulence was reported by 0.8%, 5.9%, and 0% subjects, respectively, in the celecoxib, naproxen plus omeprazole, and placebo groups. Overall, there were few problems with UGI tolerability in this study. A total of 30 subjects (9 in the celecoxib group, 12 in the naproxen plus omeprazole group and 9 in the placebo group) who did not take ASA during the trial reported mild UGI discomfort (abdominal pain,

dyspepsia or nausea) and 4 subjects in the naproxen plus omeprazole group reported moderate or severe UGI discomfort. A total of 27 subjects (9 in the celecoxib group, 12 in the naproxen plus omeprazole group and 6 in the placebo group) who did not take NSAIDs/analgesics reported mild UGI discomfort and 4 subjects in the naproxen plus omeprazole group reported moderate or severe UGI discomfort. No statistically significant treatment differences among treatment groups were observed for this last category (p=0.073) or for any of the other categories analyzed. One SAE, severe cholelithiasis, occurred during the study, and this was not related to the study medication. The results of this study indicate that celecoxib treatment is safe and well tolerated when used in the regimen prescribed by the study protocol.

Conclusion(s):

In conclusion, the results of this study indicate that there was lower incidence of small bowel/gastric lesions as determined by video capsule endoscopy in subjects treated with celecoxib (200 mg BID) than in subjects treated with naproxen (500 mg BID) plus omeprazole (20 mg QD). Celecoxib was safe and well tolerated in this study population.

Based on report completed on: 01 October 2003