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**PROPRIETARY DRUG NAME/GENERIC DRUG NAME:** Celebrex<sup>®</sup> / Celecoxib

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**NCT NO.:** 00137033

**PROTOCOL NO.:** A3191171

**PROTOCOL TITLE:** Multicenter, Randomized, Active-Controlled Comparison Study of the Incidence of Gastroduodenal Ulcers Associated with Celecoxib + Low Dose ASA Versus Naproxen + Low Dose ASA in Healthy Subjects (50 – 75 Years of Age)

**Study Center(s):** Forty-four (44) centers in the United States

**Study Initiation and Completion Dates:** 29 December 2004 to 25 July 2005

**Phase of Development:** Phase 4

**Study Objective(s):**

*Primary:* The primary objective of this study was to compare the incidence of gastroduodenal endoscopic ulcers between celecoxib 200 mg QD + aspirin (ASA) 81 mg QD versus naproxen 500 mg BID + ASA 81 mg QD in healthy subjects (50 – 75 years old).

*Secondary:* The secondary objectives of this study were to:

- Compare the incidence of gastroduodenal endoscopic ulcers between celecoxib + ASA versus placebo + ASA 81 mg in healthy subjects (50 – 75 years of age)
- Compare the incidence of gastroduodenal endoscopic ulcers between naproxen + ASA versus placebo + ASA 81 mg in healthy subjects (50 – 75 years of age)
- Assess the clinical safety of celecoxib 200 mg QD + ASA 81 mg QD, naproxen 500 mg BID + ASA 81 mg QD, and placebo + ASA 81 mg QD administered over a 7-day period

**METHODS**

**Study Design:**

This was a 7-day, multicenter, double-blind, randomized, double-dummy, placebo-controlled parallel-group study. This study was designed to assess the incidence of endoscopic upper

gastroduodenal ulcers in healthy subjects (50 – 75 years of age) when administering celecoxib 200 mg QD + ASA 81 mg QD, naproxen 500 mg BID + ASA 81 mg QD or placebo + ASA

81 mg QD. Approximately 605 eligible subjects were to be randomized to 1 of 3 regimens: celecoxib + ASA, naproxen + ASA or placebo + ASA in a 2:2:1 ratio.

There were 3 study visits: Screening (Visit 1, within 10 days prior to the first dose of study medication), Baseline/Randomization (Visit 2, Day 1) and Post-Treatment/Early Termination (Visit 3, Day 7). A telephone call was recommended on the day before the Baseline/Randomization Visit and the Post-Treatment Visit to remind subjects to prepare for the endoscopy according to their doctor's instructions. Efficacy and safety assessments were made.

### **Number of Subjects (Planned and Analyzed):**

*Planned:* The planned sample size was 605 subjects with a randomization of 2:2:1 to celecoxib + ASA, naproxen + ASA and placebo + ASA (242:242:121 subjects, respectively).

*Analyzed:* A total of 962 subjects were screened and 662 were randomized. Of the 662 randomized subjects, 1 subject in the celecoxib + ASA group was randomized but not treated.

### **Diagnosis and Main Criteria for Inclusion:**

Eligible subjects were healthy males or females, 50 to 75 years of age, who had no clinically significant findings regarding laboratory test results or physical examination, and had no gastric, pyloric channel or duodenal ulcers nor had more than 5 erosions in the stomach or duodenum (UGI endoscopic score < 4 on Mucosal Grading Scale). Subjects also could not have esophageal ulcer or erosion or active GI disease. In addition, subjects were excluded if *Helicobacter pylori* was detected by serology, or if over-the-counter or prescription NSAIDs or ASA was used within 2 weeks of the first dose of study medication.

### **Study Treatment:**

Study drug was prepared in a double-dummy fashion. Subjects were instructed to take study medication 2 times daily for 7 days. The AM dose consisted of 1 capsule from bottle "A" (celecoxib 200 mg or placebo of celecoxib), 1 capsule from bottle "B" (naproxen 500 mg or placebo of naproxen) and 1 tablet from bottle "C" (ASA 81 mg). The PM dose consisted of 1 capsule from bottle "B" (naproxen 500 mg or placebo of naproxen). The content of the capsules was dependent upon assigned treatment.

### **Efficacy Evaluations:**

Upper gastrointestinal endoscopy was used in this study to evaluate gastric, duodenal, and esophageal injuries.

*Primary:* The primary endpoint was the incidence of gastroduodenal ulcer(s). An ulcer was defined as a mucosal grade of 7 as indicated by any lesion  $\geq 3$  mm in diameter with unequivocal depth.

*Secondary:* Secondary endpoints included:

- Number of gastroduodenal ulcers
- Incidence of any gastric or duodenal ulcer (mucosal grade 7 as indicated by any lesion with unequivocal depth  $\geq 3$  mm diameter)
- Incidence of any gastroduodenal, gastric or duodenal erosion/ulcer (mucosal grade 4 – 7)
- Incidence of any esophageal ulcer or erosion/ulcer (using the traditional esophagus endoscopy evaluation [normal, erosion or ulcer] and the Los Angeles Classification of Esophageal Ulcer and Erosion [A through D])

### **Safety Evaluations:**

Safety assessments included adverse events (AEs), serious adverse events (SAEs), laboratory tests, concomitant medications, physical examinations, and reason for discontinuation.

### **Statistical Methods:**

*Efficacy:* The primary analysis population was the Endoscopy Evaluable population consisting of all randomized subjects who received at least 1 dose of study medication and had both baseline and post-treatment endoscopies. The primary efficacy analysis was the two-sided test of the equality of proportions of subjects with at least 1 gastroduodenal ulcer for celecoxib 200 mg QD + ASA 81 mg QD versus naproxen 500 mg BID + ASA 81 mg QD compared using the Cochran-Mantel-Haenszel (CMH) statistic, with stratification by center.

Analyses of secondary categorical outcome variables were carried out using the CMH statistic, with stratification by center. Each secondary efficacy variable dealing with the incidence of a lesion (gastric, duodenal or gastroduodenal of various grades) was analyzed as pairwise comparisons among the 3 treatment arms, testing the equality of proportion of subjects experiencing 1 or more lesions as measured in each of the secondary variables using the CMH statistic, with stratification by center. Comparisons were at an alpha level of 0.05. The odds ratio and relative risk was reported along with their respective 95% confidence intervals. If the number of events was small (less than 5 in either treatment group) a two-sided Fisher's Exact Test was used. An analysis to compare the number of gastroduodenal ulcers between each of the pairwise combinations of treatment groups was conducted using appropriate non-parametric techniques (Wilcoxon Rank-Sum and van Elteren tests).

*Safety:* All subjects who took at least 1 dose of study medication were analyzed for safety. Safety data were subjected to clinical review and summarized by appropriate descriptive statistics. Safety assessments (eg, AEs, laboratory tests, concomitant medications, vital signs,

physical examinations, reasons for discontinuation) were performed according to World Wide Safety (WWS) 3 requirements.

## RESULTS

### Subject Disposition and Demography:

Subject disposition is summarized in Table S1.

**Table S1 Disposition of Subjects**

|                                | Celecoxib + ASA |         | Naproxen + ASA |         | Placebo + ASA |         |
|--------------------------------|-----------------|---------|----------------|---------|---------------|---------|
|                                | n               | (%)     | n              | (%)     | n             | (%)     |
| Treated                        | 266             |         | 264            |         | 131           |         |
| Completed                      | 257             | (96.6)  | 256            | (97.0)  | 128           | (97.7)  |
| Discontinued                   | 9               | (3.4)   | 8              | (3.0)   | 3             | (2.3)   |
| Endoscopy evaluable population | 257             | (96.3)  | 257            | (97.3)  | 129           | (98.5)  |
| Safety population              | 266             | (99.6)  | 264            | (100.0) | 131           | (100.0) |
| Analyzed for Safety            |                 |         |                |         |               |         |
| Adverse events                 | 266             | (100.0) | 264            | (100.0) | 131           | (100.0) |
| Laboratory data                | 160             | (97.7)  | 260            | (98.5)  | 130           | (99.2)  |

One subject from the celecoxib + ASA group was randomized but not treated.

Safety Population: Subjects who were randomized and received at least 1 dose of study medication.

Endoscopy Evaluable Population: Subjects who were randomized, received at least 1 dose of study medication, and had baseline and post-treatment endoscopies.

Demographic characteristics of the randomized population were similar among the treatment groups. The mean age was approximately 58 years (range of 50 to 76 years) for all 3 treatment groups. The majority of subjects in the celecoxib + ASA, naproxen + ASA and placebo + ASA groups were female (61.0%, 68.2% and 57.3%, respectively) and white (76.0%, 74.6% and 73.3%, respectively). No significant differences were observed between the treatment groups for any demographic characteristics.

Reasons for discontinuation from treatment and study are summarized in the Table S2.

**Table S2 Discontinuation from Study (All Randomized Subjects)**

|                                   | Celecoxib + ASA<br>N=267 |     | Naproxen + ASA<br>N=264 |     | Placebo + ASA<br>N=131 |     |
|-----------------------------------|--------------------------|-----|-------------------------|-----|------------------------|-----|
|                                   | n                        | %   | n                       | %   | n                      | %   |
| Total discontinuations from study | 10                       | 3.7 | 8                       | 3.0 | 3                      | 2.3 |
| Related to study drug             | 2                        | 0.7 | 2                       | 0.8 | 0                      | 0.0 |
| Adverse event                     | 2                        | 0.7 | 2                       | 0.8 | 0                      | 0.0 |
| Not related to study drug         | 8                        | 3.0 | 6                       | 2.3 | 3                      | 2.3 |
| Adverse event                     | 2                        | 0.7 | 2                       | 0.8 | 1                      | 0.8 |
| Other                             | 5                        | 1.9 | 3                       | 1.1 | 1                      | 0.8 |
| Subject defaulted                 | 1                        | 0.4 | 1                       | 0.4 | 1                      | 0.8 |

One subject from the celecoxib + ASA group was randomized but not treated.

### Efficacy Results:

*Primary:*

The primary endpoint was the incidence of gastrointestinal ulcer(s). An ulcer was defined as a mucosal grade of 7 as indicated by any lesion  $\geq 3$  mm in diameter with unequivocal depth. More subjects had gastroduodenal ulcers in the naproxen + ASA group (25.3%) than in the celecoxib + ASA (7.0%) or placebo + ASA (1.6%) groups at the end of treatment. The primary comparison of gastroduodenal ulcer incidence between celecoxib + ASA and naproxen + ASA showed that subjects in the celecoxib group were less likely to develop a gastroduodenal ulcer compared with subjects in the naproxen group ( $p < 0.001$ ).

*Secondary:*

Number of Gastroduodenal Ulcers: These results are shown in Table S3.

**Table S3 Analysis of Number of Gastroduodenal Ulcers by Treatment Group (Endoscopy Evaluable Population)**

| Gastroduodenal Ulcer        | Celecoxib + ASA<br>N= 257  |          | Naproxen + ASA<br>N= 257 |          | Placebo + ASA<br>N= 129    |         |
|-----------------------------|----------------------------|----------|--------------------------|----------|----------------------------|---------|
|                             | Mean (SD)                  | 0.2      | (1.61)                   | 0.9      | (2.82)                     | 0.0     |
| Median (range)              | 0.0                        | (0 – 25) | 0.0                      | (0 – 22) | 0.0                        | (0 – 1) |
| <b>Pairwise Comparisons</b> | <b>p-value<sup>a</sup></b> |          |                          |          | <b>p-value<sup>b</sup></b> |         |
| Celecoxib vs naproxen       | <0.001                     |          |                          |          | <0.001                     |         |
| Celecoxib vs placebo        | 0.021                      |          |                          |          | 0.019                      |         |
| Naproxen vs placebo         | <0.001                     |          |                          |          | <0.001                     |         |

<sup>a</sup>Wilcoxon Rank-Sum test, normal approximation with continuity correction of 0.5.

<sup>b</sup>Van Elteren test, extension of Wilcoxon Rank-Sum in presence of blocking by center.

Ulcer is defined as a UGI mucosal endoscopy score of grade 7.

Incidence of Any Gastric or Duodenal Ulcer (Mucosal Grade 7): These results are shown in Table S4.

**Table S4 Summary of Gastric or Duodenal Ulcer (Grade 7) Incidence by Treatment Group (Endoscopy Evaluable Population)**

| Evaluation                              | Celecoxib + ASA<br>N= 257 |                      | Naproxen + ASA<br>N= 257       |        | Placebo + ASA<br>N= 129 |       |
|---|---------------------------|----------------------|--------------------------------|--------|-------------------------|-------|
| <b>Gastric Ulcers</b>                   |                           |                      |                                |        |                         |       |
| Subjects with ulcers, n (%)             | 15                        | (5.8)                | 58                             | (22.6) | 1                       | (0.8) |
| <b>Pairwise comparisons<sup>a</sup></b> |                           | <b>Relative Risk</b> | <b>95% CI of Relative Risk</b> |        | <b>p-value</b>          |       |
| Celecoxib vs naproxen                   |                           | 0.25                 | (0.15 – 0.44)                  |        | <0.001                  |       |
| Celecoxib vs placebo                    |                           | 7.75                 | (1.03 – 58.22)                 |        | 0.016                   |       |
| Naproxen vs placebo                     |                           | 28.47                | (3.98 – 203.55)                |        | <0.001                  |       |
| <b>Duodenal Ulcers</b>                  |                           |                      |                                |        |                         |       |
| Subjects with ulcers, n (%)             | 3                         | (1.2)                | 18                             | (7.0)  | 1                       | (0.8) |
| <b>Pairwise comparisons<sup>a</sup></b> |                           | <b>Relative Risk</b> | <b>95% CI of Relative Risk</b> |        | <b>p-value</b>          |       |
| Celecoxib vs naproxen                   |                           | 0.17                 | (0.05 – 0.56)                  |        | <0.001                  |       |
| Naproxen vs placebo                     |                           | 9.07                 | (1.24 – 66.33)                 |        | 0.006                   |       |

<sup>a</sup>The comparison between celecoxib and placebo demonstrated no statistical significance.

CI= Confidence interval

Ulcer is defined as a UGI mucosal endoscopy score of grade 7.

Gastroduodenal, Gastric or Duodenal Ulcer/Erosion: These results are shown in Table S5.

**Table S5 Summary of Gastroduodenal, Gastric or Duodenal Erosion/Ulcer Incidence by Treatment Group (Endoscopy Evaluable Population)**

| Evaluation                                | Celecoxib + ASA<br>N= 257 |                      | Naproxen + ASA<br>N= 257       |        | Placebo + ASA<br>N= 129 |        |
|---|---------------------------|----------------------|--------------------------------|--------|-------------------------|--------|
| <b>Gastroduodenal Erosion/Ulcer</b>       |                           |                      |                                |        |                         |        |
| Subjects with erosion/ulcer, n (%)        | 85                        | (33.1)               | 168                            | (65.4) | 31                      | (24.0) |
| <b>Pairwise comparisons</b>               |                           | <b>Relative Risk</b> | <b>95% CI of Relative Risk</b> |        | <b>p-value</b>          |        |
| Celecoxib vs naproxen                     |                           | 0.50                 | (0.41 – 0.60)                  |        | <0.001                  |        |
| Celecoxib vs placebo                      |                           | 1.41                 | (1.01 – 1.97)                  |        | 0.041                   |        |
| Naproxen vs placebo                       |                           | 2.78                 | (2.03 – 3.79)                  |        | <0.001                  |        |
| <b>Gastric Erosion/Ulcer</b>              |                           |                      |                                |        |                         |        |
| Subjects with erosion/ulcer, n (%)        | 67                        | (26.1)               | 163                            | (63.4) | 25                      | 19.4   |
| <b>Pairwise comparisons<sup>a</sup></b>   |                           | <b>Relative Risk</b> | <b>95% CI of Relative Risk</b> |        | <b>p-value</b>          |        |
| Celecoxib vs naproxen                     |                           | 0.40                 | (0.32 – 0.50)                  |        | <0.001                  |        |
| Naproxen vs placebo                       |                           | 3.33                 | (2.33 – 4.77)                  |        | <0.001                  |        |
| <b>Duodenal Erosion/Ulcer<sup>b</sup></b> |                           |                      |                                |        |                         |        |
| Subjects with erosion/ulcer, n (%)        | 25                        | (9.7)                | 61                             | (23.7) | 12                      | (9.3)  |
| <b>Pairwise comparisons</b>               |                           | <b>Relative Risk</b> | <b>95% CI of Relative Risk</b> |        | <b>p-value</b>          |        |
| Celecoxib vs naproxen                     |                           | 0.41                 | (0.27 – 0.63)                  |        | <0.001                  |        |
| Naproxen vs placebo                       |                           | 2.59                 | (1.46 – 4.58)                  |        | <0.001                  |        |

<sup>a</sup>The gastric erosion/ulcer celecoxib versus placebo comparison was nonsignificant.

<sup>b</sup>The duodenal erosion/ulcer celecoxib versus placebo comparison was nonsignificant.

Esophageal Ulcer or Erosion/Ulcer: There were no esophageal ulcers among subjects in any treatment group. The incidence of esophageal erosions was small in all 3 treatment groups;

9.3% in the celecoxib + ASA group, 7.0% in the naproxen + ASA group and 6.2% in the placebo + ASA group. None of the pairwise comparisons between treatment groups of esophageal erosion/ulcer incidence were statistically significant.

**Safety Results:**

An overview of frequent AEs is presented in Table S6.

**Table S6 Incidence of Treatment-emergent Adverse Events (All Causality) Reported in ≥ 3% of Subjects in Any Treatment Group (Safety Population)**

| Adverse Event                     | Celecoxib + ASA<br>N= 266 |     | Naproxen + ASA<br>N= 264<br>n (%) |     | Placebo + ASA<br>N= 131<br>n (%) |     |
|-----------------------------------|---------------------------|-----|-----------------------------------|-----|----------------------------------|-----|
|                                   | n                         | %   | n                                 | %   | n                                | %   |
| <b>Gastrointestinal disorders</b> |                           |     |                                   |     |                                  |     |
| Abdominal pain                    | 7                         | 2.6 | 10                                | 3.8 | 2                                | 1.5 |
| Abdominal pain upper              | 3                         | 1.1 | 15                                | 5.7 | 3                                | 2.3 |
| Constipation                      | 4                         | 1.5 | 8                                 | 3.0 | 1                                | 0.8 |
| Diarrhea                          | 9                         | 3.4 | 11                                | 4.2 | 2                                | 1.5 |
| Dyspepsia                         | 17                        | 6.4 | 17                                | 6.4 | 4                                | 3.1 |
| Flatulence                        | 6                         | 2.3 | 9                                 | 3.4 | 3                                | 2.3 |
| Hiatus hernia                     | 9                         | 3.4 | 4                                 | 1.5 | 1                                | 0.8 |
| Nausea                            | 10                        | 3.8 | 11                                | 4.2 | 3                                | 2.3 |
| Stomach discomfort                | 8                         | 3.0 | 5                                 | 1.9 | 1                                | 0.8 |
| <b>Nervous disorders</b>          |                           |     |                                   |     |                                  |     |
| Headache                          | 14                        | 5.3 | 12                                | 4.5 | 13                               | 9.9 |

If the same subject had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once in each row. Any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event for which severity was recorded. In this case, the reported severity was summarized. Includes data up to 30 days after last dose of study drug.

One subject in the celecoxib + ASA group experienced an SAE post-treatment. This subject had a carcinoid nodule (gastric adenocarcinoma) on the post-treatment endoscopy, which was not considered to be study drug related. The carcinoid nodule was considered by the investigator to be a pre-existing condition that was not identified during the baseline endoscopy due to the small size of the nodule. The nodule became apparent on the post treatment endoscopy due to the surface becoming erythematous after receiving study drug.

Discontinuations due to AEs are shown in Table S7.

**Table S7 Discontinuations Due to Adverse Events**

| Number of Subjects     | AE (MedDRA Preferred Term)  | Relationship to Study Drug  |
|------------------------|---|---|
| <b>Celecoxib + ASA</b> |   |   |
| 1                      | Abdominal pain<br>Stomach discomfort<br>Hyperhidrosis   | Related<br>Related<br>Related   |
| 1                      | Chest discomfort<br>Hiccups<br>Eructation<br>Gastroesophageal reflux disease<br>Nausea<br>Dizziness<br>Pharyngolaryngeal pain | Unrelated<br>Unrelated<br>Unrelated<br>Unrelated<br>Unrelated<br>Unrelated<br>Unrelated |
| 1                      | Muscle twitching<br>Anxiety   | Unrelated<br>Unrelated  |
| 1                      | Dyspepsia   | Related   |
| <b>Naproxen + ASA</b>  |   |   |
| 1                      | Abdominal pain  | Related   |
| 1                      | Pharyngolaryngeal pain  | Unrelated   |
| 1                      | Urticaria   | Related   |
| 1                      | Upper respiratory tract infection   | Unrelated   |
| <b>Placebo + ASA</b>   |   |   |
| 1                      | Herpes zoster   | Unrelated   |

There were no deaths in this study.

**CONCLUSION(S):**

In this 7-day, double-blind, randomized, multicenter, parallel-group study in healthy subjects, 50 to 75 years of age, who received celecoxib 200 mg QD + ASA 81 mg QD, naproxen 500 mg BID + ASA 81 mg QD or placebo + ASA 81 mg QD, the study findings were as follows:

- More subjects had gastroduodenal ulcers in the naproxen + ASA group (25.3%) than in the celecoxib + ASA (7.0%) or placebo + ASA (1.6%) groups at the end of treatment (p-value for celecoxib versus naproxen <0.001, Wilcoxon Rank-Sum test).
- The incidence of endoscopic gastroduodenal ulcers was significantly lower in subjects treated with placebo + ASA (mean 0.0 ulcers) than with celecoxib + ASA (mean 0.2 ulcers, p-value for celecoxib versus placebo= 0.021, Wilcoxon Rank-Sum test) or naproxen + ASA (mean 0.9 ulcers, p-value for naproxen versus placebo <0.001, Wilcoxon Rank-Sum test).
- In general, celecoxib was safe and well-tolerated in this study. One subject in the celecoxib + ASA group experienced an SAE post-treatment (carcinoid nodule [gastric adenocarcinoma]), which was not considered by the investigator to be related to the study drug.