RESPONSE TO NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN AFRICAN AMERICAN SUBJECTS WITH OSTEOARTHRITIS OF THE KNEE

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BACKGROUND

- The commonly reported risk factors for the incidence and progression of osteoarthritis (OA) include age, sex, hormonal status, bone density, nutrition, and obesity.[1,2] There is also increasing evidence to suggest that ethnicity and race may play an important role in the prevalence and variability of OA.[3-5]
- Recent data suggest that African Americans have a higher burden of multiple, large-joint OA and are more likely to have knee OA than white subjects.[6]
- Despite the apparent variation in prevalence and severity of OA among different racial and ethnic groups, non-white groups remain substantially underrepresented in clinical trials assessing the efficacy and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of OA.

OBJECTIVE

- To compare the analgesic effectiveness and tolerability of celecoxib, naproxen, and placebo in an African American population with OA of the knee.

METHODOLOGY

Study design

- This was a randomized, double-blind, placebo-controlled, parallel-group, noninferiority trial conducted in 28 centers in the United States.
- 322 African American subjects aged ≥ 45 years with OA of the knee in a flare state were randomized to receive celecoxib 200 mg qd, naproxen 500 mg bid, or placebo for 6 weeks.

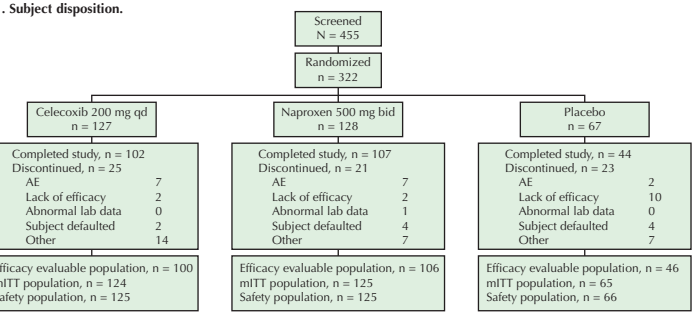
Outcome measures

- The primary efficacy outcome was the change from baseline to Week 6 in the Patient's Assessment of Arthritis Pain measured on a visual analog scale (VAS) from 0 mm (no pain) to 100 mm (worst pain).
- Secondary efficacy outcomes included:
  - Patient's and Physician's Global Assessments of Arthritis and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index from baseline to Week 6
  - Change in American Pain Society (APS) pain scores from baseline to Day 7
  - Change in Pain Satisfaction Scale from screening to Week 6
  - Change in Patient Health Questionnaire (PHQ-9) scores from screening to Week 6 to evaluate depressive syndrome
  - Measurement of upper gastrointestinal (UGI) tolerability.
- Safety was assessed by monitoring treatment-emergent adverse events (AEs), serious AEs, and physical examination.

Statistical analysis

- Primary efficacy analysis was carried out on the evaluable population (treated subjects with > 70% treatment compliance, no major protocol violations, and having both baseline and Week 6 VAS assessments).
- Secondary analyses were performed using the modified intent-to-treat (mITT) population (randomized subjects receiving > 1 dose of study medication and having > 1 postbaseline follow-up efficacy measure).

Figure 1. Subject disposition.



RESULTS

Patients

- A total of 322 subjects (80% female, mean age 58 years [range, 45-83], mean duration of OA > 5 years) were randomized, of whom 253 completed the study (Figure 1).
- 69 subjects discontinued prematurely, due to AEs, lack of efficacy, abnormal laboratory test results, protocol violation, or the subject defaulted (eg, was lost to follow-up or was no longer willing to participate). 6 randomized subjects did not take the study medication.
- Baseline demographics and clinical characteristics were similar across all treatment groups (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

	Celecoxib 200 mg qd (n = 127)	Naproxen 500 mg bid (n = 128)	Placebo (n = 67)	*P* Value
Age, y, mean ± SD (Range)	58.0 ± 8.8 (45-83)	58.0 ± 8.1 (45-79)	58.0 ± 8.8 (45-82)	0.951
Female, n (%)	102 (80)	105 (82)	51 (76)	0.611
Duration of OA, y, mean ± SD	5.4 ± 5.0	5.1 ± 5.6	6.2 ± 7.3	0.430
Patients' Global Assessment, n (%)				0.970
Very good	0	0	0	
Good	0	1 (< 1)	0	
Fair	34 (27)	28 (22)	17 (25)	
Poor	75 (59)	83 (65)	41 (61)	
Very poor	18 (14)	16 (13)	9 (13)	
Physician's Global Assessment, n (%)[a]				0.844
Very good	0	0	0	
Good	0	0	0	
Fair	33 (26)	33 (26)	18 (27)	
Poor	84 (66)	87 (69)	45 (67)	
Very poor	10 (8)	7 (6)	4 (6)	
Functional capacity classification, n (%)[a]				0.609
I	5 (4)	4 (3)	2 (3)	
II	63 (50)	75 (59)	39 (58)	
III	58 (46)	49 (38)	26 (39)	
IV	0	0	0	
VAS score, mm, mean ± SD	67.4 ± 12.7	68.4 ± 13.2	69.6 ± 12.6	0.579
WOMAC total domain score[a], mean ± SD	55.6 ± 16.2	57.7 ± 17.0	60.2 ± 14.8	0.195

[a]WOMAC total domain score is the sum of pain, stiffness, and physical function domain scores.

Efficacy outcomes

Primary outcome

- For the primary end point, the Patient's Assessment of Arthritis Pain (VAS), celecoxib was shown to be as effective as naproxen in reducing OA pain (Table 2).
- No statistically significant difference was observed between the active treatment groups and placebo.

Table 2. Patient's Assessment of Arthritis Pain (VAS) at Week 6 in the Efficacy Evaluable Population

	Celecoxib 200 mg qd (n = 100)	Naproxen 500 mg bid (n = 106)	Placebo (n = 46)
Baseline, mean ± SE	67.7 ± 1.2	68.0 ± 1.3	70.0 ± 1.8
Week 6, mean ± SE	31.5 ± 2.4	29.9 ± 2.4	36.5 ± 4.2
Change from baseline			
LS mean ± SE	-36.2 ± 2.7	-5.5 ± 4.3	-3.3 ± 4.3
(95% CI)	(-8.9 to 4.4)	(-14.0 to 2.9)	(-11.7 to 5.2)
P value	0.5060	0.1988	0.4459

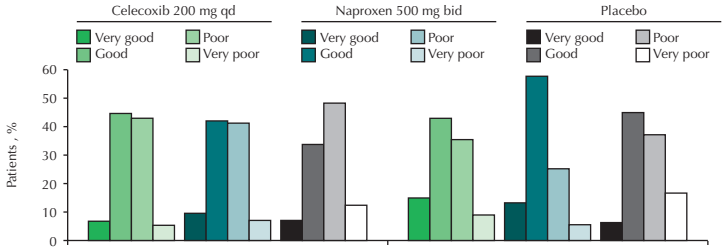
Secondary outcomes

- The percentage of subjects with OA condition "improved" from baseline was 39% (celecoxib), 45% (naproxen), and 41% (placebo) at Week 2 increasing to 49% (celecoxib), 52% (naproxen), and 46% (placebo) by the Week 6/early termination visit. Between-treatment differences were not statistically significant.
- Physicians described the arthritis condition of 52% of the subjects in the celecoxib group and 56% of the subjects in the naproxen group as "improved" by the Week 6/early termination visit. Between-treatment differences were statistically significant in favor of celecoxib and naproxen over placebo ($P = 0.047$ and $P = 0.039$, respectively) (Figure 2).
- Change from baseline in the Week 6/early termination WOMAC OA index scores did not differ significantly between the celecoxib and naproxen groups. No between-treatment differences were observed (Table 3).
- In general, APS pain scores improved from baseline to Day 7. There were no statistically significant differences between naproxen and placebo. Celecoxib was significantly different from placebo in 3 isolated instances: "any pain in the past 24 h" on Day 6 ($P = 0.017$), "pain interference in normal work" on Day 3 ($P = 0.008$), and "worst pain in 24 h" on Day 3 ($P = 0.007$).

CONCLUSIONS

- Celecoxib was as effective as naproxen in relieving pain associated with OA of the knee in African American patients.
- Few significant differences were observed between the active treatments and placebo, possibly due to a strong placebo effect.
- Celecoxib was well tolerated, with favorable UGI tolerability compared with naproxen.

Figure 2. Physician's Global Assessment of Arthritis: overall ratings (mITT population).



	P value	*P* value
Celecoxib vs naproxen	0.907	0.802
Celecoxib vs placebo	0.498	0.047
Naproxen vs placebo	0.500	0.039

- A greater percentage of subjects in the celecoxib and naproxen groups responded positively to the questions on the Pain Satisfaction Scale at the Week 6/early termination visit, compared with placebo. Mean scores of question 1 in the PHQ-9 improved in both celecoxib and naproxen groups. No differences were observed between the active treatments.

Table 3. Change From Baseline in Week 6/Early Termination WOMAC OA Index: mITT Population

Domain, LS Mean (SE)	Celecoxib 200 mg qd (n = 124)	Naproxen 500 mg bid (n = 125)	Placebo (n = 65)
Total	-22.6 (1.8)	-26.0 (1.8)	-20.8 (2.4)
Pain	-4.9 (0.4)	-5.7 (0.4)	-4.7 (0.6)
Stiffness	-1.8 (0.2)	-2.0 (0.2)	-1.5 (0.2)
Physical function	-16.0 (1.3)	-18.3 (1.3)	-14.4 (1.7)

Safety outcomes

- The incidence of treatment-related AEs was similar among the treatment groups. Treatment-related AEs occurred in 21% of subjects in the celecoxib group, 17% of subjects in the naproxen group, and 23% of subjects in the placebo group.
- The most commonly reported treatment-related AEs were depression, dizziness, and headache (Table 4).
- UGI events (moderate or severe nausea, abdominal pain, and/or dyspepsia) were experienced by a total of 10 subjects (6 in the naproxen group and 4 in the placebo group). No UGI events were reported for the celecoxib treatment group. Significant differences between treatment groups were observed in favor of celecoxib (naproxen vs celecoxib, $P = 0.029$; celecoxib vs placebo, $P = 0.013$).

Table 4. Treatment-Related AEs Occurring in ≥ 2% of Subjects

AE, n (%)	Celecoxib 200 mg qd (n = 125)	Naproxen 500 mg bid (n = 125)	Placebo (n = 66)
Depression	5 (4)	4 (3)	3 (5)
Dizziness	3 (2)	0	0
Headache	3 (2)	0	2 (3)
Diarrhea	3 (2)	2 (2)	1 (2)
Gastroesophageal reflux	3 (2)	0	1 (2)
Nausea	3 (2)	3 (2)	2 (3)
Abdominal pain	1 (1)	3 (2)	3 (5)
Dyspepsia	1 (2)	4 (3)	1 (2)

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DISCLOSURE OF INTEREST

M. N. Essex, M. O'Connell, and P. Bhadra are all employees and shareholders of Pfizer Inc.