Osteoarthritis and Cartilage 18 (2010) 629–639

Osteoarthritis and Cartilage

Efficacy and safety of naproxcinod in the treatment of patients with osteoarthritis of the knee: a 13-week prospective, randomized, multicenter study

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ARTICLE INFO

Article history:
Received 7 August 2009
Accepted 21 December 2009

Keywords:
Cyclooxygenase-inhibiting nitric-oxide donator (CINOD)
Naproxcinod
Naproxen
Non-steroidal anti-inflammatory drug (NSAIDs)
Osteoarthritis

SUMMARY

Objective: To evaluate the efficacy and safety of the cyclooxygenase-inhibiting nitric-oxide donator, naproxcinod, compared with naproxen and placebo in patients with osteoarthritis (OA) of the knee.
Method: 918 eligible patients were randomly assigned to double-blind treatment with either naproxcinod 375 mg, naproxcinod 750 mg, naproxen 500 mg or placebo, twice daily for 13 weeks. The primary objective was to show superiority of naproxcinod compared to placebo. Main efficacy criteria were assessment of pain and physical function using the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC™) and patients' overall rating of disease status (Likert scale). The main secondary objectives were to show that naproxcinod was non-inferior to naproxen 500 mg and to evaluate overall safety.
Results: Both doses of naproxcinod were statistically and clinically superior to placebo in relieving signs and symptoms of OA of the knee after 13 weeks of treatment, as demonstrated by all three co-primary endpoints ($P \leq 0.0003$). The evaluation of the other secondary efficacy measures was consistent with the primary endpoint results. Naproxcinod 750 mg was non-inferior to equimolar doses of naproxen 500 mg in the Intent-to-Treat (ITT) population. 24.5% of patients discontinued prematurely, with a higher incidence in the placebo group (18.6%) than the active groups (4.3–7.1%) discontinuing due to lack of efficacy. Both doses of naproxcinod were well-tolerated, with most adverse events being mild or moderate. Compared to placebo, naproxcinod 750 mg and 375 mg showed a similar blood pressure (BP) profile in contrast to naproxen which increased BP.
Conclusions: These results demonstrated the clinical efficacy and safety of naproxcinod in the management of the signs and symptoms of OA. Naproxcinod was well-tolerated, with BP effects similar to placebo and different from naproxen.
Clinical Trials.gov identifier: NCT00542555.

Introduction

Osteoarthritis (OA) is a common debilitating, degenerative joint disease associated with pain, swelling and loss of motion[1]. OA is a frequent cause of physical disability amongst adults and has significant socioeconomic impacts[2–5]. Given the anticipated increase in the number of OA patients, there is a need for better tolerated, more effective treatments.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage inflammation and pain, the majority of NSAID prescriptions being for OA and other musculo-skeletal conditions[2]. Cyclooxygenase (COX) enzyme inhibition is the basis for NSAID efficacy, however it also causes adverse effects, in particular blood pressure (BP) elevation, and increased risk of adverse gastrointestinal (GI) effects, which are associated with increased morbidity and mortality[6–8]. Reduced prostaglandin (PG) synthesis as a consequence of treatment with both selective and non-selective COX inhibitors may impair the systemic and renal vasodilatatory benefits of prostacyclin, leading to increases in systemic vascular resistance, sodium retention and mean arterial BP[9–15], as well as reduced gastric blood flow and mucus production, thereby increasing the risk of ulcer formation.

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1063-4584/$ – see front matter
doi:10.1016/j.joca.2009.12.013

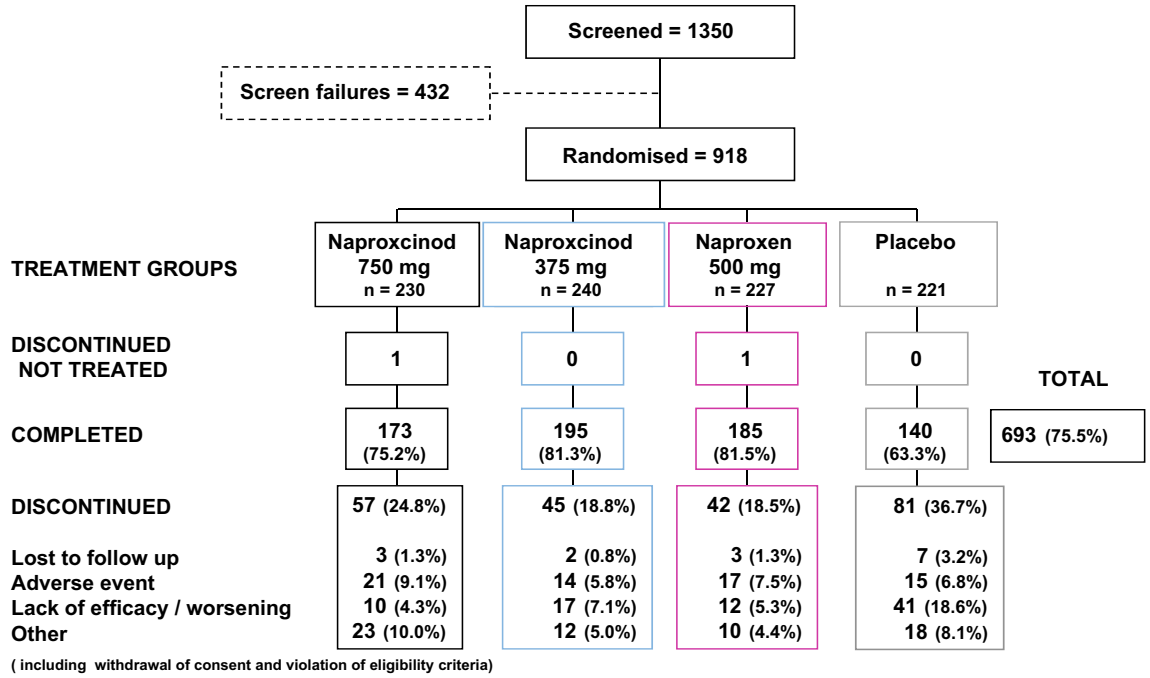

Fig. 1. Patient disposition (ITT population). Note: violation of eligibility criteria includes patients who were found not to meet the study inclusion/exclusion criteria.

Table I
Baseline characteristics (ITT population)

	Naproxcinod 750 mg bid ($N = 230$) *n* (%)	Naproxcinod 375 mg bid ($N = 240$) *n* (%)	Naproxen 500 mg bid ($N = 227$) *n* (%)	Placebo ($N = 221$) *n* (%)
Age (years), N	230	240	226	221
Mean (SD)	61.6 (9.38)	61.9 (9.21)	61.1 (9.35)	61.0 (9.02)
<65 years, *n* (%)	150 (65.2)	158 (65.8)	156 (68.7)	150 (67.9)
≥65 years, *n* (%)	80 (34.8)	82 (34.2)	70 (30.8)	71 (32.1)
Gender				
Male, *n* (%)	76 (33.0)	63 (26.3)	73 (32.2)	62 (28.1)
Female, *n* (%)	154 (67.0)	177 (73.8)	153 (67.4)	159 (71.9)
BMI (kg/m^2), N	230	240	226	220
Mean (SD)	32.8 (7.67)	33.6 (7.89)	33.0 (7.25)	33.5 (7.59)
ACR classification for global functional status				
Class I, *n* (%)	44 (19.1)	48 (20.0)	44 (19.4)	44 (19.9)
Class II, *n* (%)	130 (56.5)	134 (55.8)	126 (55.5)	121 (54.8)
Class III, *n* (%)	56 (24.3)	58 (24.2)	56 (24.7)	56 (25.3)
*Aspirin use (low dose)**				
Yes, *n* (%)	56 (24.3)	58 (24.2)	51 (22.5)	47 (21.3)
No, *n* (%)	174 (75.7)	182 (75.8)	176 (77.5)	174 (78.7)
Diabetic†				
Yes, *n* (%)	31 (13.5)	32 (13.3)	22 (9.7)	34 (15.4)
No, *n* (%)	199 (86.5)	208 (86.7)	205 (90.3)	187 (84.6)
Hypertensive‡				
Yes, *n* (%)	118 (51.3)	118 (49.2)	109 (48.0)	113 (51.1)
No, *n* (%)	112 (48.7)	122 (50.8)	118 (52.0)	108 (48.9)
Womac™ category§				
Low, *n* (%)	20 (8.7)	21 (8.8)	25 (11.0)	24 (10.9)
High, *n* (%)	210 (91.3)	219 (91.3)	201 (88.5)	197 (89.1)

There were no statistically significant differences between the groups for any of the baseline characteristics.
ACR classification: Class I – completely able to perform usual activities of daily living (self-care, vocational, and avocational); Class II – able to perform usual self-care and vocational activities, but limited in avocational activities; Class III - able to perform usual self-care activities, but limited in vocational and avocational activities; Class IV – limited in ability to perform usual self-care, vocational, and avocational activities.

* Patients on low dose aspirin were defined as those being on ≤325 mg daily aspirin (preferred term 'acetylsalicylic acid') at baseline and throughout the study.

† Diabetic patients were defined according to the patient's medical history at screening.

‡ Hypertensive patients were defined as those having medical history preferred terms of hypertension present at screening.

§ Low WOMAC™ pain score at baseline was defined as a score < 60 mm, and high WOMAC™ pain score was defined as a score ≥ 60 mm.