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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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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.
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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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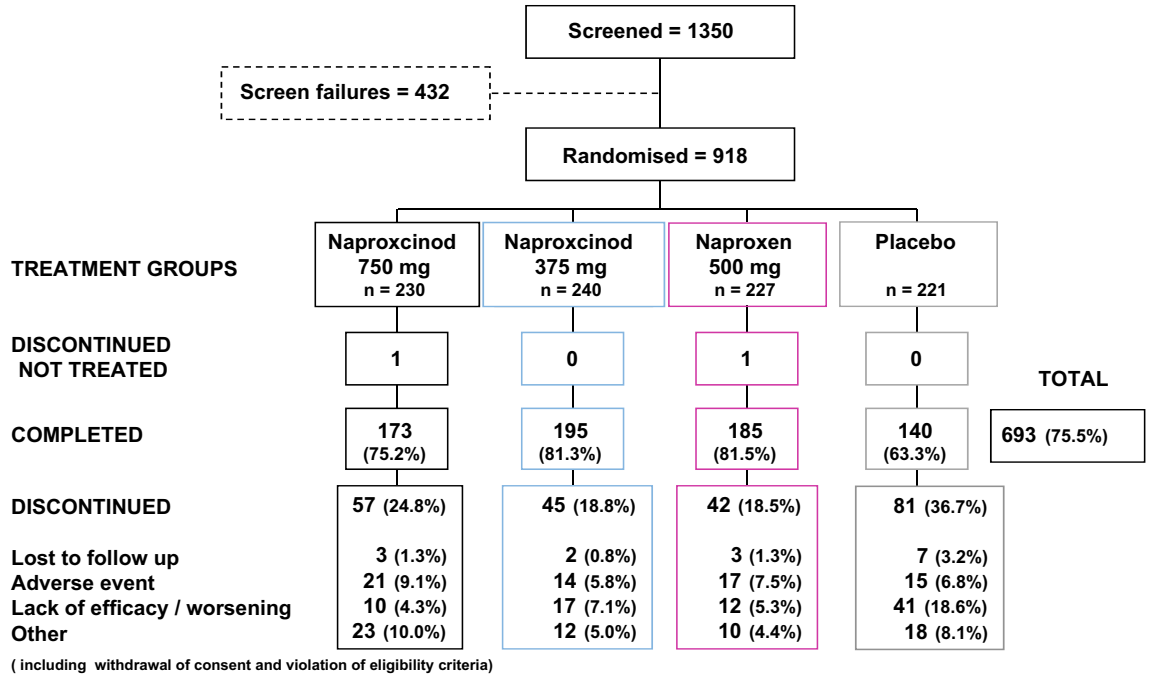

Fig. 1. Patient disposition (ITT population). Note: violation of eligibility criteria includes patients who were found not to meet the study inclusion/exclusion criteria.

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.

Naproxcinod (previously known as AZD3582) is a cyclooxygenase-inhibiting nitric-oxide (NO) donator (CINOD) with analgesic, anti-inflammatory, antipyretic and NO-donating properties. It is rapidly cleaved upon absorption to naproxen and an NO-donating moiety (data on file). Naproxcinod has been developed to provide similar efficacy to non-selective and selective NSAIDs, while providing an improved safety profile based on the release of NO which is known to have favourable effects on the cardiovascular (CV) system and protective GI effects[16,17]. NO also inhibits vascular smooth muscle proliferation and regulates interactions between leukocytes and the blood vessel wall which establish NO as a homeostatic regulator in the vasculature, the absence of which plays a role in a number of conditions and pathological states, such as hypertension and vasospasm[18,19].

In pre-clinical pharmacodynamic studies, naproxcinod dose-dependently reduced inflammatory pain, inflammatory edema, pyrogen-induced fever and blood COX activity in a manner characteristic of NSAIDs[20,21], data on file. Subsequent short-term dose-ranging clinical trials in OA demonstrated naproxcinod to have the potential for good clinical analgesic efficacy, with 750 mg bid providing maximum clinical efficacy and 375 mg bid being the lowest effective therapeutic dose[22,23]. These studies also demonstrated that naproxcinod at clinically effective doses was associated with a small decrease in supine systolic blood pressure (SBP) after 4–6 weeks of treatment, whereas SBP tended to increase in the NSAID comparator groups (naproxen and rofecoxib).

The current double-blind, randomized, multicenter, parallel-group, naproxen- and placebo-controlled study aimed to support these findings over a longer treatment period (13 weeks), and to provide more information regarding the safety of naproxcinod.

The primary objective of this study was to show that naproxcinod was superior to placebo in relieving OA signs and symptoms in patients with OA of the knee after 13 weeks of treatment. Secondary objectives were to show that naproxcinod was non-inferior in efficacy to naproxen and to evaluate the general safety, effects on BP and overall tolerability of the treatments.

Method

The study was conducted in compliance with ICH Good Clinical Practice and the Declaration of Helsinki, and its applicable amendments. It was also approved by the appropriate institutional review boards (IRBs) and patients provided written informed consent prior to participation in any study-specific procedures.

Table II
Baseline and mean change from baseline in WOMAC™ pain subscale, WOMAC™ function subscale and patient's overall rating of disease status at Week 13 for the ITT population using modified LOCF (baseline may be carried forward)

	Naproxcinod 750 mg bid ($N = 230$)	Naproxcinod 375 mg bid ($N = 240$)	Naproxen 500 mg bid ($N = 227$)	Placebo bid ($N = 221$)
WOMAC™ pain subscale score (mm)†				
Baseline				
N	229	240	226	221
Mean (SD)	73.16 (14.930)	73.58 (15.380)	71.01 (17.177)	72.15 (15.831)
Change from baseline at Week 13				
N	229	240	226	221
Mean (Std Dev)	−35.29 (27.847)	−34.62 (27.910)	−36.51 (27.194)	−24.08 (27.402)
LS Mean (SE)	−34.97 (1.755)	−34.10 (1.715)	−37.21 (1.768)	−24.24 (1.786)
95% CI*	(−38.41, −31.52)	(−37.47, −30.74)	(−40.68, −33.74)	(−27.75, −20.74)
P-value for treatment effect vs placebo*	<0.0001	<0.0001	<0.0001	–
WOMAC™ function subscale score (mm)†				
Baseline				
N	229	239	226	221
Mean (Std Dev)	71.58 (16.439)	73.06 (15.672)	71.05 (17.448)	70.39 (17.760)
Change from baseline at Week 13				
N	229	239	226	221
Mean (Std Dev)	−31.05 (27.319)	−30.19 (27.966)	−34.07 (27.159)	−20.00 (27.182)
LS Mean (SE)	−31.04 (1.740)	−29.50 (1.705)	−34.30 (1.752)	−20.53 (1.773)
95% CI*	(−34.46, −27.63)	(−32.84, −26.15)	(−37.74, −30.86)	(−24.01, −17.05)
P-value for treatment effect vs placebo*	<0.0001	0.0003	<0.0001	–
Patient's overall rating of disease status‡				
Baseline				
N	229	240	225	221
Mean (Std Dev)	1.36 (0.891)	1.41 (0.911)	1.36 (0.851)	1.38 (0.787)
Change from baseline at Week 13				
N	229	240	225	221
Mean (Std Dev)	1.25 (1.182)	1.14 (1.361)	1.40 (1.369)	0.72 (1.222)
LS Mean (SE)	1.23 (0.070)	1.16 (0.068)	1.39 (0.071)	0.72 (0.071)
95% CI*	(1.10, 1.37)	(1.03, 1.30)	(1.25, 1.52)	(0.58, 0.86)
P-value for treatment effect vs placebo*	<0.0001	<0.0001	<0.0001	–

* *P*-values and 95% CI are from pairwise contrasts from ANCOVA model with baseline as covariate and treatment as a factor.

† A negative change represents an improvement. A positive change represents a worsening. Difference is calculated as (first group − second group). Missing values imputed using the LOCF method from the previous visit, unless data were missing due to treatment-related AE drop out, in which case worst observation was used. Baseline values may have been used if necessary.

‡ A positive change represents an improvement. A negative change represents a worsening. Difference is calculated as (first group − second group). Missing values imputed using the LOCF method from the previous visit, unless data were missing due to treatment-related AE drop out, in which case worst observation was used. Baseline values may have been used if necessary.

The study was conducted from 19 December 2005–05 September 2006 (last patient visit) at 109 US centers. Males and females aged ≥40 years with primary OA of the knee, as confirmed by radiographs and the American College of Rheumatology (ACR) guidelines having global functional status I, II or III, were recruited. Patients were required to be current chronic users of NSAIDs or acetaminophen for OA pain (i.e., had used NSAIDs or acetaminophen at full therapeutic doses for at least 20 days out of 30 days during the last month prior to the screening visit) and were to have experienced a flare of pain after a discontinuation period of ≥5 half lives of a prior analgesic or anti-inflammatory therapy. Patients were excluded if they had uncontrolled hypertension or uncontrolled diabetes (as judged by the investigator), hepatic dysfunction or renal impairment at screening, recent coronary heart disease or stroke history within the preceding year, gastroduodenal bleeding or ulceration history within the prior 6 months, medical or arthritic disease that could interfere with efficacy evaluations, acute ligamentous or meniscal injury of the study joint within 2 years, arthroscopy of the study joint within 6 months, or if they were candidates for imminent joint replacement surgery (within 3 months).

Eligible patients were sequentially randomized in a 1:1:1:1 ratio using a remote system to receive one of four treatments: naproxcinod 750 mg twice daily (bid) (equimolar to naproxen 500 mg bid and with similar PK profile[24]), naproxcinod 375 mg bid, naproxen 500 mg bid or placebo bid. Rescue analgesia (acetaminophen 500 mg tablets) was provided for use in case of increased OA pain, with a maximum accepted dose of 2000 mg/day.

Efficacy was assessed at baseline and Weeks 2, 6, and 13 using the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC™) Visual Analogue Scale (VAS) for pain, stiffness, and physical function; Modified Osteoarthritis Research Society International (OARSI) responder rate (derived from WOMAC™ scores); VAS of pain intensity at rest and during walking; patients' and investigators' overall rating of disease status, treatment and response to therapy (Likert scale); and Quality of Life Short Form 36 Health Survey Questionnaire (SF-36)®. Additional efficacy measures included rescue medication use and cumulative rate of discontinuation for lack of efficacy or worsening of disease.

Safety was assessed by adverse events (AEs), BP measurements, heart rate (HR), laboratory parameters (i.e., hematology, blood chemistry and urinalysis), body mass index (BMI), and electrocardiogram (ECG) measurements. BP was measured in a rigorously standardized manner at each visit, pre-dose at baseline and 2–4 h post-morning dose of study medication and other morning medications, including anti-hypertensive treatments, at Weeks 2, 6, and 13. A total of three measurements were made by a blinded assessor using standard American Heart Association and 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7)[25,26] criteria in the sitting position using a cuff appropriate to arm size (i.e., width of 12 cm for subjects of normal stature and 15 cm for larger subjects). The examiner was to ensure that the air in the cuff was emptied between measurements.

All AEs were recorded and targeted serious AEs (SAEs) were evaluated by two independent adjudication committees (CV and GI). Compliance of study medication use was determined by pill counts and medication history was obtained at each visit.

Statistical methods

The primary efficacy analysis was based on the Intent-to-Treat (ITT) population (with last observation carried forward [LOCF]; baseline values were not carried forward), which included all randomized patients and was performed on an as-randomized basis. Sensitivity analyses were performed on the per-protocol (PP) population on an as-treated basis (the PP population included all randomized patients who had no major protocol deviations during the study). A post-hoc sensitivity analysis using modified LOCF method (with baseline carried forward) was also performed on the ITT population.

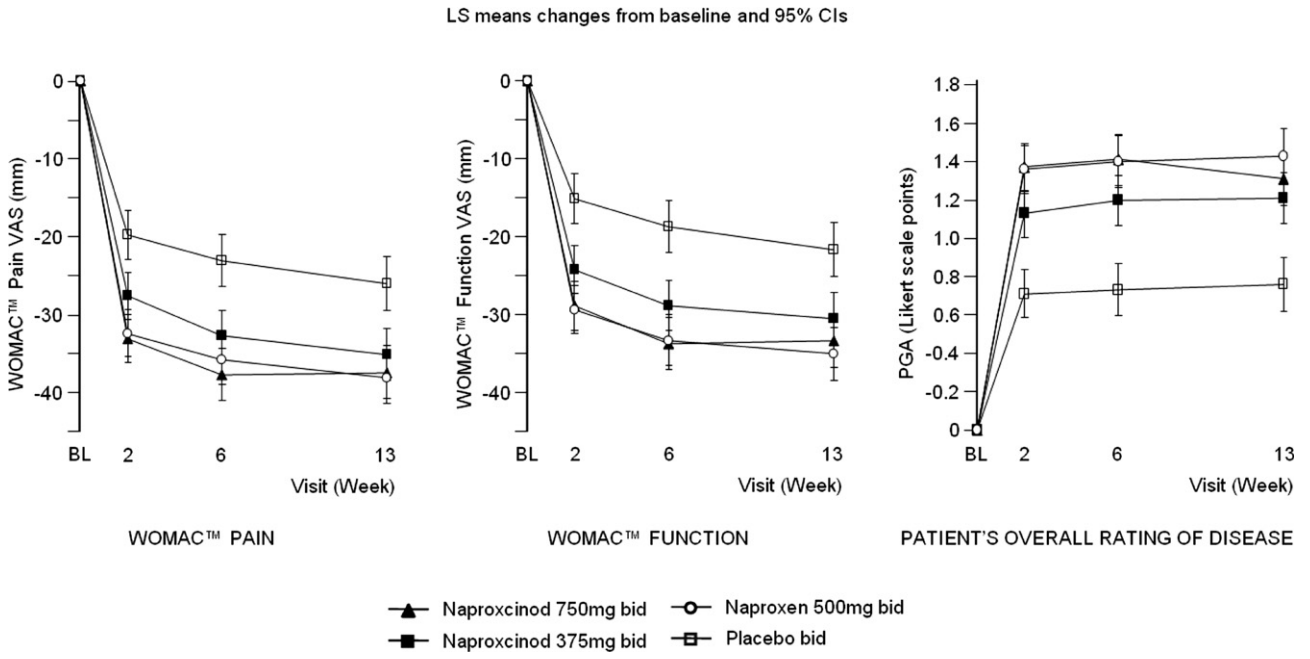

Fig. 2. LS Mean and 95% CI change from baseline to Weeks 2, 6 and 13 in WOMAC™ pain subscale, WOMAC™ function subscale and patient's overall rating of disease status (ITT population) using LOCF (without baseline carried forward). *P*-value and 95% CI are from pairwise contrasts from an ANCOVA model with baseline as covariate and with treatment as a factor. $P < 0.0001$ for all comparisons of naproxcinod 750 mg vs placebo; $P \leq 0.0004$ for all comparisons of naproxcinod 375 mg vs placebo.

The study was powered to reach statistical significance for the comparisons of both doses of naproxcinod vs placebo (superiority contrast) and vs naproxen (non-inferiority contrast) at 13 weeks. A total of 164 patients per treatment group were needed to reach 95% power to detect a difference of 8 mm (standard deviation [SD] = 20 mm) between each naproxcinod dose and naproxen in each of the two WOMAC™ variables. The same number of patients was needed to detect a difference of 0.4 (SD = 1) in patients' overall rating of disease status. These calculations were based on a one-sided two-sample *t* test with an alpha level of 0.025. Assuming a drop out rate of about 20% over the course of the trial, a total of 205 patients were needed in each treatment group. The overall power to detect a statistically significant difference for all three comparisons of the primary endpoint was at least 86% (or 95% cubed). For the superiority tests, the overall power with 205 patients per group was above 97% for all three primary comparisons together. These calculations were based on a two-sided two-sample *t* test with an alpha level of 0.05 and assuming a difference of 10 mm (SD = 20 mm) in the two WOMAC™ variables and a difference of 0.5 (SD = 1) in patients' overall rating of disease status.

Analyses were based on an analysis of covariance (ANCOVA), with treatment group as a factor and baseline as a covariate. For each analysis, a two-sided test with a significance level ≤0.05 was used. No adjustment for multiplicity was needed since all three primary efficacy variables were required to be significant based on a pre-specified stepwise order. The same ANCOVA model was used to compare each naproxcinod dose to naproxen 500 mg using both the ITT and PP populations.

Non-inferiority margins were 8 mm in the WOMAC™ pain and function subscales and 0.4 in the patient overall rating of disease status. For each non-inferiority analysis, the same ANCOVA models described for the primary efficacy analyses were used. For each analysis (naproxcinod dose group vs naproxen 500 mg bid), three

Table III
Secondary efficacy measures (ITT population)

	Naproxcinod 750 mg bid (*N* = 230)	Naproxcinod 375 mg bid (*N* = 240)	Naproxen 500 mg bid (*N* = 227)	Placebo bid (*N* = 221)
WOMAC™ composite pain, stiffness, and function subscale score (mm): change from baseline at Week 13				
N	188	198	187	145
LS Mean (SE)	−36.81 (1.795)	−35.06 (1.75)	−39.90 (1.799)	−28.03 (2.044)
Comparisons vs placebo: *P*-value	0.0013	0.0092	<0.0001	–
VAS pain intensity (mm) at rest: change from baseline at Week 13				
N	186	197	189	144
LS Mean (SE)	−37.84 (1.786)	−35.92 (1.737)	−40.51 (1.772)	−29.71 (2.032)
Comparisons vs placebo: *P*-value	0.0027	0.0205	<0.0001	–
VAS pain intensity (mm) during walking: change from baseline at Week 13				
N	186	197	189	144
LS Mean (SE)	−44.49 (1.904)	−41.82 (1.850)	−46.04 (1.890)	−34.52 (2.164)
Comparisons vs placebo: *P*-value	0.0006	0.0106	<0.0001	–
Patient's overall rating of treatment at Week 13				
N	187	202	189	146
LS Mean (SE)	2.86 (0.075)	2.84 (0.072)	2.99 (0.075)	2.34 (0.085)
Comparisons vs placebo: *P*-value	<0.0001	<0.0001	<0.0001	–
Investigator's overall rating of treatment at Week 13				
N	187	202	189	147
LS Mean (SE)	2.82 (0.074)	2.84 (0.071)	3.00 (0.074)	2.35 (0.083)
Comparisons vs placebo: *P*-value	<0.0001	<0.0001	<0.0001	–
Investigator's overall rating of disease status at Week 13				
N	186	202	188	147
LS Mean (SE)	1.38 (0.068)	1.42 (0.065)	1.53 (0.067)	1.08 (0.076)
Comparisons vs placebo: *P*-value	0.0034	0.0007	<0.0001	–
Patient's overall rating of the response to therapy at Week 13				
N	187	202	189	147
LS Mean (SE)	2.77 (0.083)	2.79 (0.079)	2.93 (0.082)	2.26 (0.093)
Comparisons vs placebo: *P*-value	<0.0001	<0.0001	<0.0001	–
Investigator's overall rating of the response to therapy at Week 13				
N	187	202	189	147
LS Mean (SE)	2.78 (0.080)	2.78 (0.077)	2.95 (0.079)	2.24 (0.090)
Comparisons vs placebo: *P*-value	<0.0001	<0.0001	<0.0001	–
Average daily number of rescue medication tablets taken				
N	222	232	219	210
LS Mean (SE)	1.43 (0.106)	1.33 (0.103)	1.34 (0.106)	1.77 (0.108)
Comparisons vs placebo: *P*-value	0.0226	0.0033	0.0042	–
SF-36® MCS score: change from baseline at Week 13				
N	184	195	185	142
LS Mean (SE)	2.78 (0.618)	2.92 (0.600)	2.58 (0.616)	1.99 (0.704)
Comparisons vs placebo: *P*-value	0.3999	0.3126	0.5288	–
SF-36® PCS score: change from baseline at Week 13				
N	184	195	185	142
LS Mean (SE)	8.52 (0.615)	7.08 (0.597)	8.98 (0.613)	5.25 (0.700)
Comparisons vs placebo: *P*-value	0.0005	0.0474	<0.0001	–

MCS = mental component score; PCS = physical component score; SE = standard error.

2-sided 95% confidence intervals (CIs) were constructed for the three primary variables respectively. If the upper limits of the CIs for mean change in WOMAC™ pain and functional subscale scores and the lower limit of the CI for the overall rating of disease fell within the corresponding specific margins, then the non-inferiority of the given naproxcinod dose against naproxen 500 mg bid was considered demonstrated.

Safety analyses were based on the safety population, which included all patients receiving at least one dose of investigational product, and were performed on an as-treated basis. Patients with multiple occurrences of an AE were counted only once in the respective AE category. Patients with multiple AEs within a particular system organ class or preferred term were counted under the category of their most drug-related and most severe AE within that system organ class or preferred term.

Planned BP analyses were based on the standard summary statistics by treatment group, as well as shift tables showing baseline and follow-up values. Post-hoc analyses were based on an ANCOVA with treatment group as a factor and baseline SBP/diastolic blood pressure (DBP) as a covariate. The analyses were performed using two-sided tests at a significance level of 5% for both comparisons vs placebo and comparisons vs naproxen.

Results

A total of 1350 patients were screened and 918 were randomized (Fig. 1). Approximately 70% of patients were female and 30% male (Table I). The mean age was 61.4 years (range: 39.6–87.8 years). Two thirds of patients (66.9%) were aged <65 years and most patients were white (83.8%). Mean height was 166.7 cm, mean weight was 92.4 kg and mean BMI was 33.2 kg/m^2. Baseline characteristics did not differ significantly between groups. Almost half of patients (49.9%) were considered hypertensive at baseline, 23.1% were taking low-dosage aspirin (≤325 mg/day) and 13% were diabetic. A total of 693 patients (75.5%) completed the study and 225 patients (24.5%) discontinued prematurely (Fig. 1). The most common reasons for discontinuation were lack of efficacy or worsening of disease, and AEs. The incidence of premature discontinuation due to lack of efficacy or worsening of disease was notably higher in the placebo group (18.6%) compared to the three active treatment groups (4.3%, 7.1%, and 5.3% in the naproxcinod 750 mg, naproxcinod 375 mg and naproxen groups, respectively [$P < 0.001$ for all groups]).

The primary efficacy parameters were the mean change from baseline to Week 13 in WOMAC™ pain and function subscale scores and the patient's rating of overall disease status. Both doses of naproxcinod were statistically significantly superior to placebo for all three co-primary efficacy endpoints ($P \leq 0.0003$) (Table II and Fig. 2). Similar results for each of the primary efficacy endpoints were seen in the PP population and ITT population using modified LOCF (Table II).

Naproxen was statistically superior to placebo for all three co-primary efficacy endpoints, thus confirming the internal sensitivity of the study. The results of subgroup analyses by center, age, gender, race, ethnicity, aspirin use, diabetic status, hypertensive status and baseline WOMAC™ pain category were consistent with the results of the primary efficacy analysis.

In the ITT population at Week 13, both doses of naproxcinod were statistically non-inferior to naproxen 500 mg regarding the change from baseline in WOMAC™ pain subscale score (based on an upper limit of the 95% CI of 8 mm). In the PP population, naproxcinod 750 mg was statistically non-inferior to naproxen 500 mg, with naproxcinod 375 mg failing to show non-inferiority compared to naproxen 500 mg. For the change from baseline in WOMAC™ function subscale score, naproxcinod 750 mg was statistically non-inferior to naproxen 500 mg, but naproxcinod 375 mg was not. In the PP population, naproxcinod 750 mg failed to show non-inferiority. Regarding the change from baseline in the patient's overall rating of disease status, naproxcinod 750 mg bid was statistically non-inferior to naproxen 500 mg, but naproxcinod 375 mg failed to achieve statistical non-inferiority to naproxen 500 mg (based on a lower limit of the 95% CI of −0.4). The PP population showed that both doses of naproxcinod were statistically non-inferior to naproxen 500 mg.

At Week 13, the modified OARSI responder rates for the three active treatments were statistically significantly superior to placebo ($P < 0.01$). No statistically significant difference between naproxen and either dose of naproxcinod was observed. Significantly more patients discontinued due to lack of efficacy/worsening of the disease in the placebo group (18.6%) than in the three active treatment groups (4.3%, 7.1%, and 5.3% for naproxcinod 750 mg, 375 mg and naproxen 500 mg, respectively) ($P < 0.001$ for each). There was no statistically significant difference between the naproxen and naproxcinod groups. Evaluation of the other secondary efficacy measures showed consistent results with the primary efficacy analyses (Table III).

Table IV
Summary of adverse events by preferred term reported in ≥2% of patients in any treatment group (safety population)

Preferred term	Naproxcinod 750 mg bid ($N = 229$) n (%)	Naproxcinod 375 mg bid ($N = 240$) n (%)	Naproxen 500 mg bid ($N = 225$) n (%)	Placebo bid ($N = 222$) n (%)
Any adverse event	108 (47.2)	98 (40.8)	127 (56.4)	86 (38.7)
Nausea	8 (3.5)	6 (2.5)	13 (5.8)	5 (2.3)
Dyspepsia	12 (5.2)	7 (2.9)	9 (4.0)	8 (3.6)
Dizziness	12 (5.2)	3 (1.3)	3 (1.3)	6 (2.7)
Constipation	4 (1.7)	5 (2.1)	11 (4.9)	1 (0.5)
Headache	2 (0.9)	11 (4.6)	6 (2.7)	6 (2.7)
Diarrhea	6 (2.6)	4 (1.7)	9 (4.0)	5 (2.3)
Edema peripheral	6 (2.6)	2 (0.8)	9 (4.0)	4 (1.8)
Arthralgia	5 (2.2)	8 (3.3)	3 (1.3)	1 (0.5)
Injury	1 (0.4)	7 (2.9)	3 (1.3)	2 (0.9)
Sinusitis	3 (1.3)	0	6 (2.7)	3 (1.4)
Upper respiratory tract infection	2 (0.9)	6 (2.5)	5 (2.2)	4 (1.8)
Abdominal pain	5 (2.2)	0	4 (1.8)	0
Bronchitis	5 (2.2)	5 (2.1)	3 (1.3)	2 (0.9)
Contusion	1 (0.4)	5 (2.1)	5 (2.2)	2 (0.9)
Cough	2 (0.9)	2 (0.8)	5 (2.2)	3 (1.4)
Rash	5 (2.2)	2 (0.8)	2 (0.9)	0
Stomach discomfort	4 (1.7)	1 (0.4)	5 (2.2)	1 (0.5)
Urinary tract infection	4 (1.7)	1 (0.4)	5 (2.2)	2 (0.9)

Mean duration of therapy was lower in the placebo group (70 days) compared to the active treatment groups (range: 79–82 days). The majority of the patients (90.4%) were compliant, although compliance was slightly lower in the placebo group.

The incidence of AEs was greater in the naproxen 500 mg group (56.4%) compared to the naproxcinod 750 mg and 375 mg groups (47.2% and 40.8%, respectively), and was lowest in the placebo group (38.7%). Most AEs were mild or moderate in severity; the AEs reported by ≥2% of patients in any treatment group are shown in Table IV.

The incidence of SAEs was low (naproxcinod 750 mg [1.7%], naproxcinod 375 mg [0.8%], naproxen [1.3%], and placebo [2.3%]) and the incidence of AEs leading to premature discontinuation was similar across groups (naproxcinod 750 mg [9.2%], naproxcinod 375 mg [5.8%], naproxen [7.6%], and placebo [6.8%]). The incidence of treatment-related AEs was similar for naproxen 500 mg (21.3%) and naproxcinod 750 mg (21.8%), and lower for naproxcinod 375 mg (14.2%) and placebo (16.7%).

At least one GI AE was reported for 17.0% of patients in the naproxcinod 750 mg group, 12.9% of patients in the naproxcinod 375 mg group, 23.6% of patients in the naproxen group, and 12.2% of patients in the placebo group. There were four GI SAEs (two GI hemorrhages in the naproxcinod 750 mg group, one ischemic colitis in the naproxen group, and one colitis in the placebo group); all were considered treatment-related. Due to the small number of events, no meaningful comparisons among groups can be made.

At least one CV AE was reported for 4.4% of patients in the naproxcinod 750 mg group, 1.7% of patients in the naproxcinod 375 mg group, 3.1% of patients in the naproxen group, and 2.7% of patients in the placebo group, with most being related to ECG changes. There were four CV SAEs (tachycardia and chest pain in one patient, and myocardial infarction in another patient in the naproxcinod 750 mg bid group, hypertension in one patient in the naproxcinod 375 mg bid group, and congestive cardiac failure in

Table V
Mean baseline and post-dose blood pressure (mmHg), and mean and LS Mean changes from baseline in blood pressure by study visit (safety population)

	Study visit			
	Baseline	Week 2	Week 6	Week 13
Systolic blood pressure (mmHg)				
Naproxcinod 750 mg bid				
N	229	221	204	188
Mean (SD)	125.45 (14.125)	123.61 (14.388)	122.02 (14.698)	121.66 (14.554)
Mean change from baseline (SD)	–	−1.93 (11.637)	−3.81 (12.135)	−3.74 (12.887)
LS Mean change from baseline (95% CI)*		−2.03 (−3.40, −0.65)	−3.92 (−5.42, −2.41)	−3.92 (−5.58, −2.27)
Naproxcinod 375 mg bid				
N	240	235	216	202
Mean (SD)	126.51 (13.196)	124.73 (13.464)	123.41 (12.629)	123.53 (14.886)
Mean change from baseline (SD)	–	−1.84 (11.624)	−3.52 (12.792)	−3.18 (12.238)
LS Mean change from baseline (95% CI)*		−1.60 (−2.93, −0.26)	−3.16 (−4.63, −1.70)	−2.85 (−4.45, −1.25)
Naproxen 500 mg bid				
N	225	220	210	188
Mean (SD)	125.59 (14.690)	125.61 (13.527)	124.67 (12.053)	124.74 (13.749)
Mean change from baseline (SD)	–	0.09 (11.294)	−0.81 (13.144)	−0.97 (13.782)
LS Mean change from baseline (95% CI)*		−0.02 (−1.40, 1.36)	−1.07 (−2.56, 0.41)	−1.03 (−2.68, 0.62)
Placebo bid				
N	222	213	181	147
Mean (SD)	125.97 (12.872)	124.71 (13.931)	122.71 (14.659)	122.57 (13.701)
Mean change from baseline (SD)	–	−0.99 (10.918)	−3.38 (11.376)	−2.94 (11.690)
LS Mean change from baseline (95% CI)*		−1.04 (−2.44, 0.36)	−3.38 (−4.98, −1.78)	−3.07 (−4.94, −1.20)
Diastolic blood pressure (mmHg)				
Naproxcinod 750 mg bid				
N	229	221	204	188
Mean (SD)	76.99 (9.077)	74.87 (9.372)	74.48 (10.048)	74.49 (8.717)
Mean change from baseline (SD)	–	−2.10 (7.329)	−2.72 (7.908)	−2.67 (8.156)
LS Mean change from baseline (95% CI)*		−1.97 (−2.89, −1.05)	−2.51 (−3.52, −1.50)	−2.44 (−3.50, −1.38)
Naproxcinod 375 mg bid				
N	240	235	216	202
Mean (SD)	76.62 (8.673)	75.34 (9.290)	74.01 (8.892)	74.41 (9.032)
Mean change from baseline (SD)	–	−1.23 (7.906)	−2.53 (8.559)	−2.15 (8.832)
LS Mean change from baseline (95% CI)*		−1.25 (−2.15, −0.36)	−2.60 (−3.58, −1.62)	−2.20 (−3.22, −1.18)
Naproxen 500 mg bid				
N	225	220	210	188
Mean (SD)	76.61 (8.290)	75.89 (8.401)	75.50 (8.576)	75.94 (8.049)
Mean change from baseline (SD)	–	−0.64 (7.906)	−1.06 (8.160)	−0.58 (8.408)
LS Mean change from baseline (95% CI)*		−0.67 (−1.60, 0.25)	−1.12 (−2.11, −0.12)	−0.65 (−1.71, 0.41)
Diastolic blood pressure (mmHg)				
Placebo bid				
N	222	213	181	147
Mean (SD)	76.67 (8.901)	76.16 (8.207)	75.32 (8.060)	75.29 (8.919)
Mean change from baseline (SD)	–	−0.29 (7.681)	−1.17 (8.101)	−1.08 (8.449)
LS Mean change from baseline (95% CI)*		−0.36 (−1.30, 0.58)	−1.26 (−2.33, −0.19)	−1.22 (−2.42, −0.02)

* LS Mean changes (95% CI) were obtained from an ANCOVA with treatment as fixed effect and baseline SBP/DBP as a covariate.

one patient in the placebo group). None were considered treatment-related. Two patients (one in the naproxcinod 375 mg group and one in the naproxen group) had abnormal ECG readings at study exit that, in the opinion of an independent, blinded cardiologist, may be due to experiencing a clinically 'silent' myocardial infarction during the study. Based on so few events, no meaningful comparison among groups can be made.

There were few potentially hypotension-related AEs reported (pre-defined by the Data Safety Monitoring Board), the most common of these being dizziness, reported in 5.2% of patients in the naproxcinod 750 mg group; 1.3% of patients in the naproxcinod 375 mg group; 1.3% of patients in the naproxen group; and 2.7% of patients in the placebo group.

With respect to BP, small reductions were seen from baseline in mean SBP following treatment with naproxcinod 750 mg, naproxcinod 375 mg and placebo (Least Square [LS] Mean changes [95% CI] at Week 13: −3.92 [−5.58, −2.27], −2.85 [−4.45, −1.25], and −3.07 [−4.94, −1.20] mmHg, respectively), whereas in the naproxen group there was no notable change from baseline (LS Mean changes [95% CI] at Week 13: −1.03 [−2.68, 0.62] mmHg). The difference in LS Mean changes showed that naproxcinod 750 mg decreased SBP statistically significantly more compared with naproxen 500 mg (difference in LS Mean changes [95% CI]: −2.89 [−5.23, −0.55]; $P = 0.0154$). Furthermore, there were small reductions from baseline in mean DBP with naproxcinod 750 mg, naproxcinod 375 mg and placebo (LS Mean changes [95% CI] at Week 13: −2.44 [−3.50, −1.38], −2.20 [−3.22, −1.18] and −1.22 [−2.42, −0.02] mmHg, respectively) compared with almost no change from baseline with naproxen (LS Mean changes [95% CI] at Week 13: −0.65 [−1.71, 0.41] mmHg). The difference in LS Mean changes showed that both naproxcinod 750 mg and 375 mg doses decreased DBP statistically significantly more compared with naproxen 500 mg (difference in LS Mean changes [95% CI]: −1.79 [−3.29, −0.29]; $P = 0.0193$ and −1.55 [−3.03, −0.08]; $P = 0.0386$). The SBP and DBP reductions seen in the naproxcinod groups were apparent from Week 2 onwards, with the effect then being maintained throughout the 13 weeks of treatment (Table V and Fig. 3).

Other assessments comprising HR, ECG, BMI, hematology, blood chemistry, and urinalysis, revealed no safety concerns in any treatment group.

Discussion

Naproxcinod, a CINOD anti-inflammatory drug designed for treatment of chronic pain, is rapidly cleaved to naproxen and an NO-donating moiety. Naproxen inhibits both COX-1 and COX-2 enzymes and is an effective anti-inflammatory and analgesic agent. CINODs have been designed to overcome the adverse effects arising from chronic NSAID administration by exploiting the positive effect of NO on the GI and CV systems.

Results from this study showed that naproxcinod 375 mg bid and 750 mg bid were statistically superior to placebo in relieving the signs and symptoms of OA after 13 weeks of treatment, as evidenced by all three co-primary endpoints and secondary efficacy measures. Benefits were sustained over time and were of a magnitude accepted as clinically significant for pain relief[27], with the mean differences between the groups in the WOMAC™ pain subscale VAS ranging from 9 to 12 mm. Similar trends were observed in the subgroups of age, gender, race or baseline pain level.

The efficacy of naproxcinod showed dose-dependency, with the 750 mg bid dose providing greater improvements at all timepoints and for all variables. This finding concurs with results from earlier OA phase II trials in which efficacy and safety of a range of doses of naproxcinod from 125 mg to 1125 mg bid were assessed. Naproxcinod 125 mg bid failed to show efficacy whereas all doses ≥375 mg bid were efficacious. Importantly, no additional benefit was observed with doses of naproxcinod at 1125 mg bid compared to 750 mg bid[23]. These efficacy results correspond with recent guidelines for OA management, suggesting a stepwise therapeutic approach starting with the lowest effective dose. The potential for two different doses of naproxcinod demonstrating clinical efficacy provides dosing flexibility just as with naproxen and ibuprofen, the most widely used NSAIDs.

Study limitations include the fact that subjects were only followed for 13 weeks of treatment, and efficacy and safety evaluation

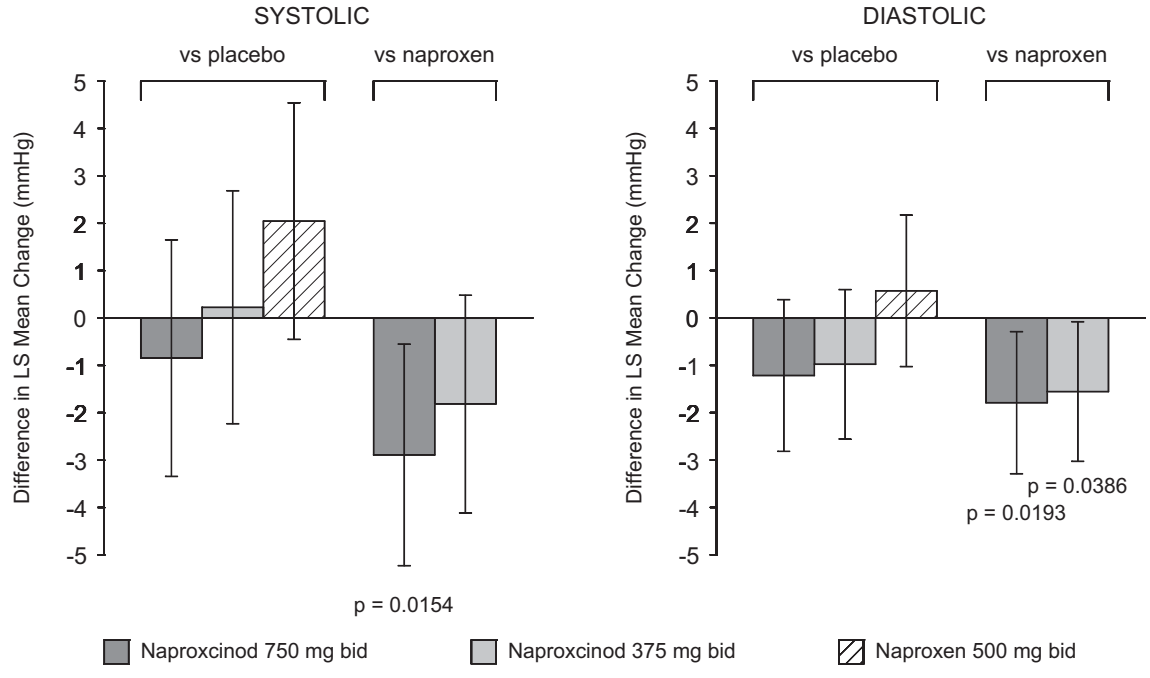

Fig. 3. Difference in LS Mean changes (95% CI) from baseline in post-dose SBP and DBP at Week 13 (safety population).

over longer time periods will be necessary. The flare design utilized is standard for such trials, but does not mimic the usual clinical setting, although it does permit better distinction of efficacy, and the inclusion of a widely used positive control used in treating OA provides a benchmark. Additionally, although subjects were drawn from a general OA population, screening criteria excluded certain sub-groups. Finally, one cannot exclude selective discontinuations which could have an impact on the results. Strengths of the study include the completeness of data collection and standardization of BP measurements.

The choice of NSAID is often dictated by safety considerations, particularly as patients with OA often have clinically important co-morbidities. CINODs were specifically developed to provide the potential for greater GI and CV safety than seen with existing NSAIDs. NO is known to have important physiologic and potentially beneficial pharmacologic actions on both the GI and CV systems; the challenge has been to develop a means of delivering sustained NO activity to the target tissues, in contrast with existing organic nitrates which have both a rapid onset and generate tolerance to their activity. Non-clinical pharmacology studies with CINODs have clearly demonstrated an activity attributed to NO in both the GI and CV systems. Non-clinical studies comparing naproxcinod with naproxen have shown increased GI blood flow, increased mucus production, reduced leukocyte adherence and gastroprotection[21]. Other investigations have reported marked beneficial effects of naproxcinod on BP in several different murine models of hypertension. The results of all these studies were consistent with a prolonged and sustained NO activity in animal experiments.

The concept of decreased GI-damaging properties of naproxcinod in comparison with naproxen has been supported by the results from two 12-day studies on gastric mucosal injury in healthy volunteers and a 6-week endoscopy trial in subjects with OA[24,28,29].

In this study, naproxcinod 750 mg showed a comparable general safety and tolerability profile to naproxen 500 mg. Naproxcinod 375 mg showed a similar safety and tolerability profile compared with placebo and appeared to have a better safety and tolerability profile than naproxcinod 750 mg and naproxen 500 mg. Naproxcinod was generally well-tolerated, with only a small number of potential NO mechanism-based events, particularly dizziness, reported at the higher dose. Dizziness has also been reported with other NSAIDs[30]. No difference between the groups in early discontinuation due to AEs, particularly due to hypotension-related AEs was noted. Few serious GI or CV AEs were reported, with no major imbalance among the groups; however, because of the small number of events, the possibility of a difference cannot be excluded. Larger and longer trials will need to be undertaken to obtain a more accurate determination of the GI and CV safety of naproxcinod.

In previously reported phase 2 OA studies[22,23,28], subjects treated with naproxcinod consistently showed a small decrease in BP compared to subjects treated with placebo, contrasting with increases in BP observed in subjects treated with naproxen or rofecoxib. This phase 3 trial comprised a larger group of patients that is considered representative of the general OA population, and confirms the earlier findings of a differential BP response with naproxcinod compared to naproxen. Naproxcinod 750 mg and naproxcinod 375 mg showed reductions from Baseline in SBP at Weeks 2, 6 and 13 that were similar in magnitude to SBP changes seen in the placebo group. In contrast, naproxen increased SBP compared to placebo, with the difference in SBP between the naproxcinod 750 mg group and the naproxen 500 mg group being statistically significant.

These results observed with naproxcinod are clinically relevant. In this study, the efficacy of naproxcinod was clearly demonstrated, with naproxcinod 750 mg bid being non-inferior to equimolar doses of naproxen 500 mg bid. The overall safety profile of 750 mg of naproxcinod was similar to that of 500 mg of naproxen, with the 375 mg naproxcinod and placebo groups having fewer safety issues reported. As naproxen is generally considered one of the safer NSAIDs from a CV perspective[31–33], the BP changes following treatment with naproxcinod compared to naproxen may provide an additional factor reducing CV risk.

As approximately 50% of the OA population has concurrent hypertension, the availability of an agent like naproxcinod that does not appear to increase BP compared to placebo, unlike other NSAIDs, has the potential to address an important medical need. Further studies, including those specifically focusing on the longer-term safety of naproxcinod and its effects on BP throughout the day (e.g., ambulatory BP monitoring [ABPM]) and over longer periods of time will guide its future use in OA patients.

Conflict of interest

Dr Schnitzer reports receiving research support from the National Institutes of Health, Pfizer Laboratories Inc, Wyeth Laboratories, Nordic Biosciences, Novartis Pharmaceuticals Inc, Genzyme and Pozen. Dr Schnitzer presently serves as a consultant to Logical Therapeutics Inc, NicOx, Merck & Co Inc, Santosolve, Solstice and Horizon Therapeutics and is a non-invested shareholder of NicOx SA.

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Supplementary material

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