

# Clinical trial: comparison of ibuprofen–phosphatidylcholine and ibuprofen on the gastrointestinal safety and analgesic efficacy in osteoarthritic patients

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## SUMMARY

### Background

Chronic use of NSAIDs is associated with gastrointestinal (GI) toxicity that increases with age.

### Aim

To evaluate the GI safety and therapeutic efficacy of ibuprofen chemically associated with phosphatidylcholine (PC) in osteoarthritic (OA) patients.

### Methods

A randomized, double-blind trial of 125 patients was performed. A dose of 2400 mg/day of ibuprofen or an equivalent dose of ibuprofen-PC was administered for 6 weeks. GI safety was assessed by endoscopy. Efficacy was assessed by scores of analgesia and anti-inflammatory activity. Bioavailability of ibuprofen was pharmacokinetically assessed.

### Results

Ibuprofen-PC and ibuprofen provided similar bioavailability/therapeutic efficacy. In the evaluable subjects, a trend for improved GI safety in the ibuprofen-PC group compared with ibuprofen that did not reach statistical significance was observed. However, in patients aged >55 years, a statistically significant advantage for ibuprofen-PC treatment vs. ibuprofen in the prevention of NSAID-induced gut injury was observed with increases in both mean Lanza scores and the risk of developing >2 erosions or an ulcer. Ibuprofen-PC was well tolerated with no major adverse events observed.

### Conclusion

Ibuprofen-PC is an effective osteoarthritic agent with an improved GI safety profile compared with ibuprofen in older OA patients, who are most susceptible to NSAID-induced gastroduodenal injury.

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## INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used to treat patients with osteoarthritis (OA). Chronic high-dose use of NSAIDs is associated with significant morbidity and mortality. NSAID-induced gastrointestinal (GI) toxicity has been estimated to result annually in approximately 107 000 hospitalizations and 16 500 deaths in the US alone.<sup>1</sup> The prevalence of NSAID-induced gastroduodenal injury has been estimated to be 20–40% in chronic users with the predominant damage (>85%) occurring in the stomach. Approximately 2% of these patients with endoscopic ulcers may present with serious clinically relevant gastroduodenal ulcers and haemorrhage.<sup>2</sup> With greater than 100 million NSAID prescriptions in 2004 in the US alone, the risk of NSAID-induced GI toxicity risk remains a serious issue.<sup>3</sup>

The choice and use of NSAIDs and gastroprotective agents have been driven by effective pain and inflammation relief in the context of risk factors. Among various risk factors, age is an important driver of NSAID intolerance.<sup>2</sup> Age (>60 years) is associated with five times greater risk for NSAID-induced GI injury than observed in an age-matched population not chronically consuming NSAIDs.<sup>4</sup> More recently, Hippisley-Cox *et al.*<sup>5</sup> have confirmed that all NSAIDs, including cyclooxygenase-2 (COX-2) selective agents (coxibs), have an increased risk of GI toxicity that increases with age. Many osteoarthritic patients have multiple risk factors, making them more susceptible to NSAID-induced peptic ulcer disease over all compared with the general population. Therefore, there is a great unmet need for efficacious NSAIDs that can safely be used in OA patients, especially those of increased age, which as discussed previously, is an independent risk factor for NSAID-induced peptic ulcer disease.<sup>2, 5</sup>

Various approaches have been used to decrease the risk of NSAID-induced GI toxicity such as the use of coxibs, and the combined use of traditional NSAIDs and gastroprotective or antisecretory agents such as misoprostol or proton pump inhibitors.<sup>6–9</sup> The recent withdrawal of multiple coxibs, as a result of concerns about their cardiovascular toxicity,<sup>10, 11</sup> demonstrates the need for additional NSAIDs with reduced GI toxicity.

Surface injury to the gastric mucosa also renders the tissue abnormally permeable to back-diffusion of luminal acid as originally described by Davenport<sup>12</sup> for aspirin. NSAIDs have been demonstrated to disrupt the gastric mucosal barrier by a COX-independent

pathway that rapidly compromises the acid resistive properties of the tissue.<sup>13</sup> As will be discussed in more detail later, we have obtained compelling preclinical evidence<sup>14–16</sup> and positive data from a short-term pilot clinical trial in healthy subjects<sup>17</sup> that preassociation of NSAIDs with phosphatidylcholine (PC) can protect the GI mucosa from the injurious action of ibuprofen and related NSAIDs. These observations served as the basis for the current clinical trial.

Ibuprofen-PC is an oil emulsion of ibuprofen and soy-derived PC that has been softgel encapsulated. In this work, a phase II trial was designed to evaluate the therapeutic efficacy and GI safety of ibuprofen-PC vs. ibuprofen at therapeutic doses to treat OA. In a randomized, multi-centre, blinded clinical trial, equivalent doses of active ibuprofen (prescription Motrin; McNeil, Ft Washington, PA, USA) and ibuprofen-PC formulations were compared. The primary endpoint of this study was to compare the incidence and severity of Motrin and ibuprofen-PC induced endoscopically observable gastroduodenal erosions/ulcers using the Lanza scoring method.<sup>18</sup> Secondary endpoints of the study were to assess and compare the analgesic and anti-inflammatory activity of treatments using Western Ontario and McMaster Universities Arthritic Criteria (WOMAC) and a visual analogue scale (VAS); the bioavailability of ibuprofen by pharmacokinetic (PK) analyses; and the overall safety of the treatments based on physical examination, laboratory tests and the incidence rates of adverse events.

## METHODS

### Drugs

Ibuprofen-PC formulation in softgel encapsulated oil suspension was provided by PLx Pharma Inc., Houston, TX, USA. The proprietary formulation contained 1:1 w/w of ibuprofen acid (BASF Corp., Mt Olive, NJ, USA) and Phosal 35SB (American Lecithin, Oxford, CT, USA) together with small amounts of compendial excipients as required by the manufacturer (Cardinal Health, Somerset, NJ, USA) for softgel encapsulation. Phosal 35SB contains ~35% w/w PC.

### Subjects and scoring

One hundred and twenty-five OA patients requiring anti-inflammatory agents (age range 18–83) with minimal or no baseline evidence of damage to the gastric

and duodenal mucosa as observed under baseline endoscopy were enrolled at six centres, whose respective Institution Review Boards had previously approved the outlined protocol. Informed Consent was obtained from each subject at enrolment. Endoscopic damage was assessed by using the Combined Lanza Endoscopic Scoring System prior to and after a 6-week course of 2400 mg/day of Motrin or 2400 mg/day of active ibuprofen in ibuprofen-PC. Lanza score is a categorical score (0–4) of endoscopic upper GI erosions, ulcers and mucosal haemorrhage defined as follows: score 0 = normal stomach and proximal duodenum; 1 = mucosal haemorrhages only; 2 = one or two erosions; 3 = three to 10 erosions; 4 = greater than 10 erosions or an ulcer.<sup>18</sup> Erosions were defined as flat white-based mucosal breaks of any size, and ulcers were defined as mucosal breaks of 3 mm or more demonstrating unequivocal depth. Minimal damage was defined as Lanza score of 2 or less. Patients with mucosal damage of grades 0, 1 and 2 were eligible for enrolment in the study.

*Inclusion/exclusion criteria.* Patients  $\geq 18$  years of age who had OA of the knee and/or hip requiring NSAID therapy were included in the study. Subjects were excluded from the study, if they had previous ulcer disease, gastro-oesophageal reflux disease within the prior 6 months, a baseline Lanza score of  $>2$ , use of NSAIDs within 2 weeks of enrolment, use of MAO inhibitors or any pain medication other than over-the-counter acetaminophen (paracetamol), the use of gastro-protective agents (including proton pump inhibitors and H<sub>2</sub>-receptor antagonists) within 3 days or any other significant concomitant health problem other than OA, notably GI problems including ulcers, frequent indigestion or heartburn (within the past 6 months). Females of child-bearing age unwilling to use adequate contraception for the duration of the study and pregnant or nursing females were not eligible. Patients with a hypersensitivity to lecithin, aspirin, ibuprofen or any other NSAID were also excluded from the study.

## Study design

The study objectives were to evaluate the GI safety, overall safety and efficacy of ibuprofen-PC vs. ibuprofen. The primary safety endpoint was change in gastroduodenal Lanza scores over baseline within

treatment groups. Other safety endpoints were: incidence of endoscopic gastroduodenal ulcers (with and without symptoms); adverse events; and changes in various clinical and laboratory assessments. The primary efficacy endpoint was change from baseline in the WOMAC subscale scores within the treatment groups. Other efficacy analyses included differences in the WOMAC scores between treatment groups and changes from baseline in the patients' VAS assessments and the bioavailability of ibuprofen using several key PK parameters.

Patients with informed consent were randomized to treatment with prescription Motrin or ibuprofen-PC, 800 mg of active ingredient three times a day (2400 mg of ibuprofen/day). At pre-enrolment, all patients underwent a physical exam, laboratory evaluation of haematology, blood chemistry and, if relevant, a pregnancy test. The medical history and use of any concomitant medications were collected. Endoscopies were performed at baseline and after 6 weeks. Every 2 weeks on protocol, patients were evaluated for pain and inflammation using the WOMAC and VAS scores and, to monitor compliance, pill counts were assessed. Adverse events and the use of concomitant medications were monitored throughout the study.

*Endoscopy.* Baseline endoscopy was performed no more than 7 days before initiating the study medication and the findings were compared with the endoscopic score after 6 weeks on treatment. All endoscopists were blinded to the treatment group. To minimize subjective interpretation, all endoscopic images were also scored by a blinded central assessor (Frank L. Lanza). Any conflicts were resolved through an adjudication process to determine a consensus score. A change of Lanza score of  $>2$  over baseline was considered clinically significant. Using this criterion, patients would have to develop a Lanza score of 2 (1 or 2 erosions), if their gastroduodenal mucosa showed no evidence of injury, Lanza score of 0 (no erosions and/or no mucosal haemorrhages) at baseline; or alternatively developed 10 or more erosions and/or an ulcer, if they had the maximal allowable Lanza score of 2 (1 or 2 erosions) at baseline.

*Pain and inflammation assessment.* The Western Ontario and McMaster Universities Arthritis Criteria Index is an extensively validated, self-administered

questionnaire that is widely used to assess OA-related disability of the knee or hip. The WOMAC assessment was performed on day 0 and at follow-up visits on weeks 2, 4 and 6.

To evaluate the relative change in pain and inflammation relief over baseline, Patient Global Assessment using a VAS was measured. Patients were asked to evaluate his/her overall assessment of treatment efficacy by making a mark on a VAS. The scale ranged from 'Great Worsening' on one end of the scale to 'Great Improvement' on the other. The VAS assessment was performed at follow-up visits on weeks 2, 4 and 6.

**Bioavailability.** On day 0 (baseline) and week 4, patients were administered their randomized study treatment and blood samples were drawn at the following time points: 0 (predose), 45, 60, 75, 90 and 120 min. Sera were prepared, coded and sent to Med-Tox Labs (St Paul, MN, USA) for ibuprofen analysis by HPLC.

**Adverse events.** Drug-related adverse events were categorized into unlikely, possible, probable or definitely treatment-related based on investigator decision using version 3.0 of the Common Terminology Criteria for Adverse Events of the National Institutes of Health (<http://ctep.info.nih.gov>). Patients were encouraged to report adverse events spontaneously or in response to general nondirected questioning. An adverse event was diagnosed as a symptomatic ulcer only if a clinically relevant ulcer (mucosal lesion >3 mm in diameter with depth) was observed under endoscopy at the 6-week time point and the patient complained of epigastric pain consistent with a diagnosis of having a peptic ulcer.

**Statistical analysis.** In this study, three analysis populations were utilized: intent to treat (ITT), evaluable for efficacy and evaluable for GI toxicity. All patients who received at least one treatment were included in the ITT population. Inclusion in the two evaluable groups was dependent on study compliance (which was based upon the subjects' following the preset requirement of both taking the test medication as directed and not taking prohibited medications).

The primary efficacy analysis consisted of the individual subscales of the WOMAC (pain, physical function, joint stiffness) and the total score compared with

the findings at baseline. For each subscale and the total score, the percentage change from baseline was calculated by subtracting the score at each follow-up visit from the score at baseline, dividing by the baseline score and multiplying by 100.

For testing within each treatment group separately, the paired *t*-test was used to compare the percentage change from baseline in WOMAC scores at each follow-up visit.

For secondary efficacy analyses, a manner similar to that used for the primary efficacy analyses was employed to investigate differences in the WOMAC between treatment groups. Differences between treatment groups were analysed using the *t*-test to determine if the percentage change from baseline in the WOMAC scores at each follow-up visit was significantly different between the two treatment groups.

For the VAS assessment, within each treatment group separately, a paired *t*-test was used to determine if the patient's VAS assessment of treatment efficacy was statistically significantly different from zero. Differences between treatment groups were analysed using the *t*-test to determine if the assessment of efficacy was significantly different between the two treatment groups.

All 125 patients were included in the analyses of adverse events and the changes in laboratory assessments, physical exams and vital signs. Analysis of Lanza scores was performed by calculating the raw change from baseline at week 6. The data designated as the change in gastric or duodenal lesion score refers to the most severely affected area within a subject. The Lanza data failed to be normally distributed, thus nonparametric statistics were utilized. Within each treatment group separately, a signed-rank test was used to determine if the patient's Lanza score was statistically significantly different at week 6 compared with day 0 (baseline). Differences between treatment groups were analysed using the rank-sum test to determine if the assessment of safety was significantly different between the two treatment groups.

**Subgroup analysis.** Age is a known risk factor in NSAID-induced GI toxicity. Prognostic factor testing using ANOVA methods revealed a borderline statistically significant interaction between patient age and treatment in relation to the change in Lanza score ( $P$ -value = 0.0726, ANOVA). Upon determination that age and treatment had a significant interaction, two population

cohorts of  $\leq 55$  and  $>55$  population were defined using the median age of the ITT population. Each cohort was independently evaluated for efficacy, PKs, Lanza score and adverse events.

## RESULTS

### Patient disposition/demographics

Patients were required to have a history of OA requiring nonsteroidal anti-inflammatory agents. A total of 125 patients were enrolled in the study, and 108 patients completed the study. The demographics of the ITT population are detailed in Table 1. No significant difference in the ITT population based on age, gender, BMI, race or other factors listed in Table 1 was observed. The evaluable population for GI safety had demographics similar to those of the ITT population, the details of which have not been provided in the table for brevity. The reasons for study dropout in the ibuprofen group (seven of 64) were as follows: 4 – withdrew consent; 1 – adverse event unrelated to

treatment; 2 – lost to follow-up. The reasons for dropout in the ibuprofen-PC group (10/61) were as follows: 4 – withdrew consent; 1 – adverse events unrelated to treatment; 3 – noncompliant; 2 – other (1 – lost to follow-up, 1 – withdrew due to diarrhoea, based upon the subject's and not the investigator's discretion). The dropout rates between treatment groups were not statistically different. None of the patients was excluded from the evaluable-for-GI-toxicity population for having a high baseline Lanza score. The reasons for the exclusion from the evaluable-for-GI-toxicity population were limited to: lost to follow-up; refusal to perform the 6-week endoscopy and failure to remain compliant with the study drug.

### Endoscopic results

In the total evaluable population for GI toxicity, the mean as well as the percentage of patients who developed multiple gastroduodenal lesions or a lesion score of  $>2$  in the ibuprofen and ibuprofen-PC groups were not significantly different (Tables 2 and 3). The primary

Table 1. Subject demographics by treatment group and age

Population	Overall		55 and under		Over 55	
	Ibuprofen (n = 64)	Ibuprofen-PC (n = 61)	Ibuprofen (n = 33)	Ibuprofen-PC (n = 31)	Ibuprofen (n = 31)	Ibuprofen-PC (n = 30)
Intent to treat						
Mean age (years)	54.1 $\pm$ 12.6	54.2 $\pm$ 13.5	44.5 $\pm$ 9.0	44.1 $\pm$ 10.2	64.3 $\pm$ 6.1	64.8 $\pm$ 6.7
Age range (years)	27–74	18–83	27.0–55.0	18.0–55.0	56.0–74.0	56.0–83.0
Gender						
Male	27 (42.2)	26 (42.6)	13 (39.4)	14 (45.2)	14 (45.2)	12 (40.0)
Female	37 (57.8)	35 (57.4)	20 (60.6)	17 (54.8)	17 (54.8)	18 (60.0)
Race						
White	27 (42.2)	33 (54.1)	10 (30.3)	13 (41.9)	17 (54.8)	20 (66.7)
Hispanic or Latino	26 (40.6)	21 (34.4)	14 (42.4)	13 (41.9)	12 (38.7)	8 (26.7)
Black	11 (17.2)	6 (9.8)	9 (27.3)	4 (12.9)	2 (6.5)	2 (6.7)
Native Hawaiian or Islander	0 (0.0)	1 (1.6)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)
BMI at first dose (kg/m <sup>2</sup> )	31.2 $\pm$ 6.9	30.6 $\pm$ 6.9	32.8 $\pm$ 7.6	32.3 $\pm$ 7.7	29.5 $\pm$ 5.7	28.8 $\pm$ 5.7
Reason for termination						
Completed study	57 (89.1)	51 (83.6)	31 (93.9)	24 (77.4)	26 (89.3)	27 (90.0)
Subject withdrawal	4 (6.2)	4 (6.6)	1 (3.0)	3 (9.7)	3 (9.7)	1 (3.3)
Unrelated adverse event	1 (1.6)	1 (1.6)	0 (0.0)	1 (3.2)	1 (3.2)	0 (0.0)
Noncompliance	0 (0.0)	3 (4.9)	0 (0.0)	2 (6.5)	0 (0.0)	1 (3.3)
Other	2 (3.1)	2 (3.3)	1 (3.0)	1 (3.2)	1 (3.2)	1 (3.3)
Evaluable for GI toxicity	(n = 58)	(n = 49)	(n = 30)	(n = 23)	(n = 28)	(n = 26)
Mean age (years)	54.1 $\pm$ 12.6	54.6 $\pm$ 13.6	44.6 $\pm$ 9.1	43.7 $\pm$ 11.1	64.3 $\pm$ 5.9	64.3 $\pm$ 6.0

Values are expressed in mean  $\pm$  s.d. or n (%).

**Table 2.** Mean and median change in gastric or duodenal lesion score

	<i>n</i>	Mean age ± s.d.	Age range	Mean change ± s.d.	Median change	Rank-sum <i>P</i> -value
Total evaluable						
Ibuprofen	58	54.1 ± 12.6	27–74	1.6 ± 1.4	2	
Ibuprofen-PC	49	54.6 ± 13.6	18–79	1.3 ± 1.4	1	
Ibuprofen						
55 and under	30	44.6 ± 9.1	27–55	1.2 ± 1.4	1	
Over 55	28	64.3 ± 5.9	56–74	2.0 ± 1.4	2	0.0353*
Ibuprofen-PC						
55 and under	23	43.7 ± 11.1	18–55	1.4 ± 1.6	1	
Over 55	26	64.3 ± 6.0	56–79	1.2 ± 1.4	1	0.7643

The total evaluable population described here and the subsequent figures represent the intention-to-treat population minus the dropouts.

\* Statistically significant (*P*-value < 0.05) vs. osteoarthritic patients using the same study medication <55 years of age.

**Table 3.** Percentage of patients with a change in gastric or duodenal lesion score of >2

	Change <2 <i>n</i> (%)	Change >2 <i>n</i> (%)	Fisher's exact test
Total evaluable			
Ibuprofen	40 (69.0)	18 (31.0)	0.2713
Ibuprofen-PC	39 (79.6)	10 (20.4)	
55 and under cohort			
Ibuprofen	24 (80.0)	6 (20.0)	0.5217
Ibuprofen-PC	16 (69.6)	7 (30.4)	
Over 55 cohort			
Ibuprofen	16 (57.1)	12 (42.9)	0.0148*
Ibuprofen-PC	23 (88.5)	3 (11.5)	

The total evaluable population described here represents the intention-to-treat population minus the dropouts.

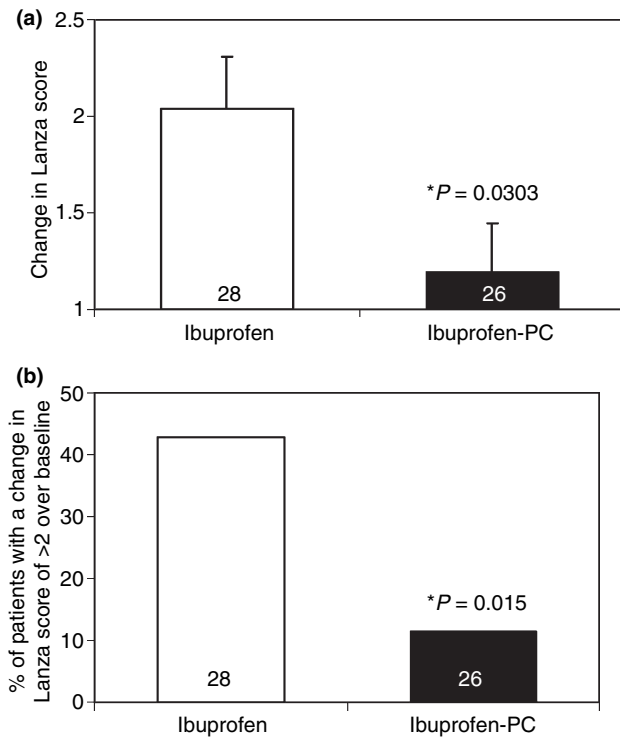
\* Statistically significant (*P*-value < 0.05) comparing ibuprofen vs. ibuprofen-PC in evaluable osteoarthritic subjects >55 years of age.

preplanned analysis did not find a statistically significant difference in the increase in Lanza scores over baseline between the two treatment groups in the total evaluable population (mean ± s.d. were 1.6 ± 1.4 in the ibuprofen group vs. 1.3 ± 1.4 in the ibuprofen-PC group; *P* = 0.24). Although not statistically different, this trend favours the experimental treatment group. This trend justified further subgroup analysis of the data, which was performed on a *post hoc* basis.

**OA patients >55 years of age.** Age is a known risk factor for NSAID-induced GI toxicity.<sup>19, 20</sup> To

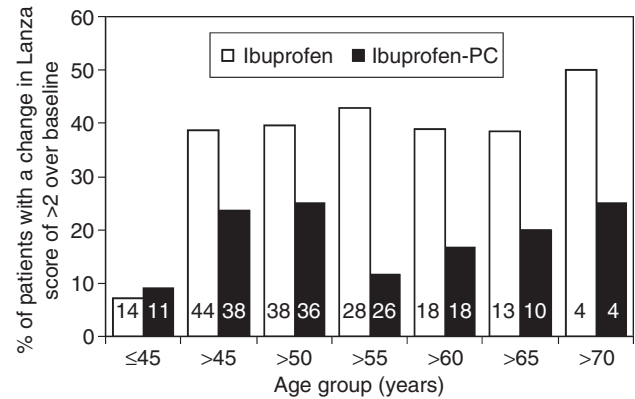
determine the effect of age on the change in Lanza score, a prognostic factor analysis was performed. Using ANOVA methods, a borderline statistically significant interaction between treatment and age as a categorical variable was observed, split into two groups at the median age of 55, relative to changes in Lanza Scores (*P*-value = 0.0726, ANOVA). Using this criterion, two subsets (≤55 and >55 years of age) were analysed. The mean change in Lanza score in patients older than the median age (55 years of age) was analysed as a subset; a statistically significant advantage for ibuprofen-PC treatment in the prevention of NSAID-induced gut injury was observed as depicted in Figure 1a. The results of the effect of age and the mean and median change in Lanza score in the various subsets are summarized in Tables 2 and 3. The mean change in gastroduodenal lesion score in ibuprofen-treated subjects was significantly higher in the >55 years group than in the ≤55 years group (Table 2; *P*-value = 0.0353, rank-sum). In contrast, no such age-dependent increase in gastroduodenal lesion score was discernible in OA patients treated with ibuprofen-PC (*P* = 0.76, rank-sum).

Within the ibuprofen-treated patients (Table 3), the relative risk of multiple gastroduodenal erosions, with an increase in Lanza score >2, in the cohort of patients >55 years was 2.15 times more likely (or a 114.5% increased risk) than patients ≤55 years, and is consistent with reports in the literature that with increasing age, more gastroduodenal damage is observed with chronic NSAID exposure.<sup>2</sup> Interestingly, within the ibuprofen-PC-treated patients (Table 3), the cohort of patients >55 had a risk ratio of 0.38 or a 62.0%



**Figure 1.** Graphic depiction of the endoscopic findings in the clinically relevant subgroup of osteoarthritic (OA) patients aged >55 years. Ibuprofen at a dose of 2400 mg/day was associated with a statistically significant difference in: (a) the increase (mean  $\pm$  S.E.M.) in mean Lanza score over baseline; (b) the increase in the percentage of patients with multiple gastroduodenal erosions/ulcers (change in Lanza scores >2) in comparison with OA patients of comparable age taking an equivalent (NSAID) dose of ibuprofen-PC over the 6-week study period. These results demonstrate that older OA patients taking ibuprofen were 3.7 times more likely to develop multiple gastroduodenal erosions/ulcers than those taking an equivalent (anti-arthritis) dose of ibuprofen-PC.

decreased risk of developing multiple gastroduodenal erosions than patients  $\leq 55$  years. As depicted in Figure 1b, the percentage scores of patients who developed gastroduodenal lesion score of >2 were 42.9 and 11.5 in the ibuprofen and ibuprofen-PC groups respectively in the >55 age cohort and were statistically significantly different ( $P$ -value = 0.0148, Fisher's exact). In this subset of patients over the age of 55 years, ibuprofen-treated patients were 3.7 times more likely (or a 270% increased risk) to develop multiple gastroduodenal erosions than the ibuprofen-PC-treated patients in the cohort. This cohort had a mean age of 64 and was similar in all relevant demographics



**Figure 2.** Comparison of the percentage of patients in the two treatment groups with multiple gastroduodenal erosions/ulcers (change in Lanza scores >2) using different age cut-offs. It can be appreciated that ibuprofen consistently caused a greater percentage of subjects to sustain more severe gastroduodenal injury (Lanza score >2) than those treated with ibuprofen-PC in subjects older than 45 years of age.

listed in Table 1. We have also compared the change in Lanza score of >2 using other age cut-offs, as depicted in Figure 2. This finding supports the case that ibuprofen consistently caused a greater percentage of subjects to sustain more severe gastroduodenal injury (Lanza score >2) than those treated with ibuprofen-PC, in accordance with this endoscopic criterion in groups of patients aged more than 45 years of age. Collectively, these data indicate that ibuprofen-PC reduced the age-related increase in NSAID-induced gastroduodenal lesions.

Additionally, one or more endoscopic ulcers were observed in 17/125 (13.6%) of the ITT population, with 12/64 in the ibuprofen-treated group (18.8%) and only five of 61 (8.2%) in the ibuprofen-PC group at the study end. Ulcer symptoms were recorded in four of 12 subjects in the ibuprofen group (33%) with an endoscopic ulcer vs. one of five (20%) subjects in the ibuprofen-PC group with one or more endoscopic ulcers. The number of patients with an endoscopic ulcer without symptoms was eight of 64 (12.5%) in the ibuprofen group and four of 61 (6.6%) in the ibuprofen-PC group. These differences in ulcer incidence, however, did not reach statistical significance, presumably because of the small size of this pilot trial. Unlike the Lanza scores outlined above, no age-dependent increase in ulcer incidence (with or without symptoms) was observed in either treatment population.

### Treatment-related adverse events other than GI erosions/ulcers

The percentage of first occurrence of adverse events (other than gastroduodenal erosions and ulcers) that were possibly, probably or definitely treatment related is summarized in Table 4. Only two serious adverse events were reported in the trial; both patients were in the ibuprofen-PC group (two of 61, 3.3%). These serious adverse events were considered unrelated to study treatment by the investigators. One serious adverse event was fracture of the left leg and the other was an episode of syncope, amnesia and dizziness associated with acute sinusitis. Both these events required hospitalization.

The GI-related adverse events other than gastroduodenal erosions and ulcers were: dyspepsia (6.3% ibuprofen vs. 14.8% ibuprofen-PC) and diarrhoea (1.6% ibuprofen vs. 9.8% ibuprofen-PC), neither of which showed significantly different rates between the two treatment groups. The noted ibuprofen-PC associated diarrhoea and dyspepsia were transient

**Table 4.** Treatment-related adverse events, other than erosions and ulcers (intention-to-treat population)

Adverse event	Ibuprofen (n = 64)	Ibuprofen-PC (n = 61)
<b>General</b>		
Abdominal pain	3 (4.7)	3 (4.9)
Fatigue	1 (1.6)	0 (0.0)
Headache	1 (1.6)	1 (1.6)
<b>Digestive</b>		
Anorexia	0 (0.0)	1 (1.6)
Diarrhoea	1 (1.6)	6 (9.8)
Dry mouth	0 (0.0)	1 (1.6)
Dyspepsia	4 (6.3)	9 (14.8)
Flatulence	0 (0.0)	1 (1.6)
Gastric reflux	0 (0.0)	1 (1.6)
Nausea	0 (0.0)	4 (6.6)
<b>Nervous</b>		
Dizziness	0 (0.0)	1 (1.6)
<b>Respiratory</b>		
Pharyngitis	0 (0.0)	1 (1.6)
Sinusitis	1 (1.6)	0 (0.0)
<b>Skin and appendages</b>		
Rash	1 (1.6)	0 (0.0)

Values presented are n (%).

It should be noted that none of the adverse event incidence rates was determined as statistically significant by treatment group.

and self-resolved, with a median duration of 4.5 and 8.0 days respectively. Other adverse events that were observed only in the ibuprofen group were: *Helicobacter pylori*-associated gastroenteritis (n = 1), GI haemorrhage (n = 1) and papulous gastropathy (n = 1).

Hypertension, which occurred in only 1.6% of the patients taking ibuprofen and 3.3% of the patients taking ibuprofen-PC, was the only cardiovascular event reported in more than one patient, and no serious cardiovascular adverse events were observed. Considering the recent attention to cardiovascular risk associated with COX-2 inhibitors, it is important to note that both ibuprofen and ibuprofen-PC were not associated with serious cardiovascular adverse events in this study. These data are consistent with the better cardiovascular safety profile generally attributed to NSAIDs over coxibs and the fact that this study was of relatively short duration.<sup>11</sup>

None of the haematology or blood chemistry assessments showed any statistically significant differences between treatment groups and no trends were discernable. Analysis of various lipid indices also did not reveal any statistically significant differences between the treatment groups.

Physical examinations and vital sign determinations were performed to evaluate safety in the ITT population. No clinically significant abnormal findings were noted for either type of assessment.

### Ibuprofen-PC and ibuprofen had similar efficacy in treating OA

Efficacy was evaluated using the WOMAC and VAS assessments for detection of improvement in OA symptoms. As summarized in Table 5, with regard to the changes in WOMAC total scores in the evaluable-for-efficacy population of patients, both treatment groups showed statistically significant improvement over baseline at each study visit. These results were consistent with the subscales for pain, joint stiffness and physical function. Similar positive results were seen in the >55 years of age subset, where both ibuprofen-PC and ibuprofen significantly decreased WOMAC scores of osteoarthritic patients (not shown). These data were also consistent with VAS assessment of overall improvement in physical functionality over baseline. Ibuprofen and ibuprofen-PC provided statistically significant improvements over baseline at each study visit. At 6 weeks, ibuprofen-treated patients had a (mean  $\pm$  s.d.) VAS improvement score of  $22.7 \pm 20.3$ ,

**Table 5.** Summary of percentage change from baseline in WOMAC total score in all patients evaluable-for-efficacy population

Visit	Treatment	n	Mean*	s.d.	P-value	
					Paired t-test	t-test
Week 2	Ibuprofen	61	-40.3	35.2	<0.0001†	0.4033
	Ibuprofen-PC	49	-35.0	30.0	<0.0001†	
Week 4	Ibuprofen	56	-45.5	40.0	<0.0001†	0.8945
	Ibuprofen-PC	52	-44.6	32.1	<0.0001†	
Week 6	Ibuprofen	57	-52.0	37.3	<0.0001†	0.8911
	Ibuprofen-PC	49	-53.0	33.7	<0.0001†	

t-tests were performed between the two treatment groups for each visit.

\* A negative percentage change indicates improvement for that subscore.

† Statistically significant vs. baseline ( $P$ -value < 0.05).

and ibuprofen-PC group showed a VAS improvement score of  $24.4 \pm 15.6$ , both of which were highly statistically significantly different ( $P < 0.001$ ) over baseline. Both treatment agents provided similar analgesic and anti-inflammatory activity based on VAS and WOMAC scores that were not significantly different.

### Ibuprofen-PC has similar bioavailability to ibuprofen

Pharmacokinetic analyses revealed that the two study medications had equivalent ibuprofen bioavailability at baseline and week 4, with regard to  $C_{max}$ ,  $t_{max}$  and  $AUC$  (Table 6). Intergroup differences in these key PK parameters were minimal among the two treatment

groups and were not statistically significantly different, although it appeared that  $C_{max}$  was modestly increased and  $t_{max}$  decreased in the ibuprofen-PC group vs. ibuprofen. It, however, should be noted that the predose and postdose ibuprofen levels were consistently higher at week 4 than at baseline, presumably because of an accumulation of the NSAID in biological fluids over the study period.

### DISCUSSION

The present study evaluated gastroduodenal mucosal injury and therapeutic efficacy of ibuprofen and ibuprofen-PC at a dose of 2400 mg/day of active ingredient for 6 weeks in OA patients. The rationale for this approach, which was briefly described earlier, is based upon evidence that: (i) the gastric mucosa of both laboratory animals and humans possess nonwettable, hydrophobic characteristics that are attributable to surface-active phospholipids, notably PC within or on the surface of the mucus gel layer;<sup>13, 14</sup> (ii) NSAIDs have a chemical affinity to associate with PC, and in doing so, induce a rapid attenuation of the surface hydrophobic barrier properties of the stomach;<sup>13-16</sup> and (iii) NSAIDs preassociated with either synthetic or natural (soy) PC were found to be less toxic to the GI tract of rodents and human volunteers evaluated in a 4-day crossover pilot clinical trial.<sup>15, 17</sup> Ibuprofen was selected as a representative NSAID to associate with PC to examine its GI safety in this longer (6 week) study, as it is commonly used by OA patients and is known to induce reproducible therapeutic efficacy and gastroduodenal injury when administered at an anti-arthritic dose of 2400 mg/day.<sup>1-5</sup>

In this study, it was determined that in the total evaluable population of OA patients aged 18-81 years

**Table 6.** Pharmacokinetics of ibuprofen and ibuprofen-phosphatidylcholine after initial dose and repeated administration over 4 weeks in evaluable patients

Treatment	PK parameter	Day 0		Week 4	
		n	Mean $\pm$ s.d.	n	Mean $\pm$ s.d.
Ibuprofen	$C_{max}$ (mg/L)	64	53.0 $\pm$ 20.0	59	58.6 $\pm$ 19.3
Ibuprofen-PC	$C_{max}$ (mg/L)	61	62.5 $\pm$ 24.8	54	71.0 $\pm$ 21.1
Ibuprofen	$t_{max}$ (min)	64	80.6 $\pm$ 27.5	59	81.7 $\pm$ 28.0
Ibuprofen-PC	$t_{max}$ (min)	61	76.7 $\pm$ 27.6	54	76.3 $\pm$ 25.1
Ibuprofen	$AUC_{0-t}$ (mg/L/min)	64	4120 $\pm$ 1839	59	4663 $\pm$ 1835
Ibuprofen-PC	$AUC_{0-t}$ (mg/L/min)	61	4583 $\pm$ 2187	54	5089 $\pm$ 1910

PC, phosphatidylcholine.

of age, ibuprofen-PC was similar to ibuprofen with regard to both bioavailability and efficacy to treat arthritis symptoms, while reducing the NSAID's ability to induce gastroduodenal erosions and ulcers; however, in this total evaluable population, the GI-protective effect did not reach statistical significance. As anticipated, ibuprofen alone induced significant gastroduodenal injury comparable to previous observations.<sup>21</sup> Interestingly, upon *post hoc* analysis, it was determined that ibuprofen-PC was safer in patients aged >55 years (with a mean age of 64 years) who are most at risk of developing NSAID-induced gastroduodenal injury. In this clinically relevant subgroup, ibuprofen-treated patients had a significantly greater absolute change in Lanza scores and were 3.7 times more likely (or a 270% increased risk) to develop multiple gastroduodenal erosions (Lanza score >2) than the ibuprofen-PC-treated patients. Although we did evaluate treatment differences using other age cut-offs as demonstrated in Figure 2, the >55 years comparison was used for statistical reasons, as it represented the median age of the study population and meaningful statistical analyses of the older age groups could not be accomplished because of the small number of subjects in these subgroups.

Numerous pilot studies have used erosions as surrogate markers of ulcers that have been linked to life-threatening GI perforation and haemorrhage. The rate of erosions of ibuprofen-PC appears to be consistent with the rate of erosions found in trials using meloxicam, rofecoxib, celecoxib and the combination of naproxen/cimetidine.<sup>18, 21–24</sup> As the latter agents have been shown to have lower ulcer rates than traditional NSAIDs, erosions may be an important surrogate marker of ulcers. In a more conservative approach, only the frequency of multiple erosions or a Lanza score of >2 was compared. The reduction in such gastroduodenal lesions accurately predicted the GI safety of rofecoxib as assessed by the reduction in perforations, haemorrhage and other outcome measures, suggesting that improvement afforded by the PC formulation of ibuprofen may be clinically relevant and warranting further testing.<sup>6, 21</sup> It should be noted that although performing *post hoc* analyses on a subset of the study population is not ideal, we do believe that the rationale for evaluating the effects of our treatment on the cohort of subject aged >55 years who are most characteristic of OA patients at risk of developing NSAID-induced GI adverse events is sound. Clearly, the use of an endoscopic study using a Lanza scoring method as

an index of GI toxicity of a test drug has limitations and the definitive demonstration of the GI safety of ibuprofen-PC will have to await future clinical outcome studies performed over an extended dosing period (1–2 years) in a large population of OA subjects.

This improved safety of ibuprofen-PC was observed at therapeutic doses for the treatment of OA. When administered at a dose of 2400 mg/day of the NSAID for 6 weeks, ibuprofen provided clear anti-inflammatory and analgesic activity over baseline. As expected, the therapeutic effectiveness of ibuprofen-PC was comparable to that of ibuprofen as assessed by both WOMAC and VAS scoring systems. These data are consistent with the results of pharmacokinetic analyses performed at baseline and at week 4. There was no indication of significant accumulation or a depot effect during chronic administration of ibuprofen-PC over that of ibuprofen, although there was a suggestion of a small yet comparable accumulation of the NSAID in biological fluids in both patient populations during a period of chronic dosing.

Ibuprofen-PC was well tolerated with no marked changes in the incidence of adverse events, compared with ibuprofen. While there appears to be a trend that total evaluable OA patients taking ibuprofen-PC had fewer symptomatic clinically diagnosed gastric ulcers than encountered in patients taking the equivalent dose of ibuprofen as indicated above, more comprehensive studies are warranted to validate these initial observations. An apparent increase in the rate of dyspepsia and diarrhoea was noted. Although this may have been caused by a general shift to milder (non-ulcer) GI symptoms in OA patients taking ibuprofen-PC, the possibility of co-administering 2400 mg/day of NSAID-associated lecithin oil along with ibuprofen in the proprietary formulation, as a contributing factor, cannot be eliminated. The relatively low incidence of diarrhoea (<10%) with ibuprofen-PC and its transient nature (duration of <5 days) may not represent a major compliance issue for chronic administration of ibuprofen-PC.

The mechanism of age-related NSAID-induced GI toxicity remains unknown. However, age associated decreases in surface hydrophobicity, prostaglandin levels and impaired healing may contribute to the deterioration of the barrier property of the mucosa. Interestingly, Hacklesberger *et al.* observed an age-related decrease in surface hydrophobicity in the antrum of the stomach, which is also the primary site of NSAID-induced ulcers.<sup>25</sup>

Phosphatidylcholine is the major surfactant phospholipid that confers surface hydrophobic characteristics to the gastric mucosa. It is possible that with age, surface phospholipid levels decrease below a critical threshold and this reduction contributes to age-related NSAID intolerance. Although the mechanism of the age-specific decrease in gastroduodenal erosions afforded by the ibuprofen-PC formulation remains unknown, this protection may be consistent with the proposed mechanism of PC-mediated protection against NSAID-induced GI toxicity. Our working hypothesis is that ibuprofen, when administered as PC-enriched lecithin oil, forms mixed micelles, which prevent the NSAID from interacting with host phospholipids within or on the luminal surface of the mucus gel layer. Without barrier disruption, NSAID-induced acid back-diffusion into the mucosa would be reduced. Below a critical level of intrinsic surfactant phospholipids within or coating the mucus gel layer, the administration of NSAIDs chemically preassociated with PC may be beneficial in mitigating NSAID-induced surface injury to the gastroduodenal mucosa and the subsequent development of erosions and ulcers. Irrespective of the mechanism, ibuprofen-PC appears significantly safer than ibuprofen in osteoarthritic patients 55 years of age and older, who are most at risk of developing NSAID-induced gastroduodenal injury and hence this novel NSAID formulation warrants additional clinical testing.

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