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Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone

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SUMMARY

Background
Gastroprotective co-therapy may reduce the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, but adherence is suboptimal.

Aim
To compare the incidence of gastric ulcers with PN 400 [enteric-coated (EC) naproxen 500 mg and immediate-release esomeprazole 20 mg], or EC naproxen.

Methods
Two randomized, double-blind, multicentre studies (PN400-301, PN400-302). Patients [stratified by low-dose aspirin (≤325 mg) use] aged ≥50 years or 18–49 years with a history of ulcer, received PN 400 BID (301, $n = 218$; 302, $n = 210$) or EC naproxen 500 mg BID (301, $n = 216$; 302, $n = 210$) for 6 months. The primary endpoint was the cumulative incidence of endoscopic gastric ulcers.

Results
The cumulative incidence of gastric ulcers was significantly lower with PN 400 vs. EC naproxen (301: 4.1% vs. 23.1%, $P < 0.001$; 302: 7.1% vs. 24.3%, $P < 0.001$). PN 400 was associated with a lower combined incidence of gastric ulcers vs. EC naproxen in low-dose aspirin users ($n = 201$) (3.0% vs. 28.4%, $P < 0.001$) and non-users ($n = 653$) (6.4% vs. 22.2%, $P < 0.001$). The incidence of, and discontinuations due to, upper gastrointestinal (UGI) AEs was significantly lower with PN 400 relative to EC naproxen ($P < 0.01$, both studies).

Conclusions
PN 400 significantly reduces the incidence of gastric ulcers, regardless of low-dose aspirin use, in at-risk patients, and is associated with improved UGI tolerability relative to EC naproxen (ClinicalTrials.gov, NCT00527782).

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INTRODUCTION

Chronic musculoskeletal diseases are highly prevalent and, with an ageing population, their incidence is increasing.[1–3] Nonsteroidal anti-inflammatory drug (NSAID) therapy is one of the mainstays of treatment for the signs and symptoms of osteoarthritis,[4–7] but the impact of tolerability issues on long-term use is of considerable clinical concern in day-to-day practice. Chronic NSAID use is associated with a risk of upper gastrointestinal (UGI) injury and toxicity,[7–9] ranging from endoscopic gastric ulcers in 15–30% of NSAID users,[10] to clinically relevant symptomatic ulcers and serious ulcer complications in 2–4% of users annually.[9, 11] Well-established risk factors for such complications include advancing age, history of ulcers or UGI symptoms, high dose of NSAID and use of certain concomitant medications [corticosteroids, anticoagulants and low-dose aspirin (LDA; 75–325 mg)].[12, 13]

Co-prescribed proton pump inhibitors (PPIs) have been demonstrated to be an efficacious strategy for reducing the risk of NSAID-associated endoscopic ulcers in at-risk patients.[14–16] Based on these data coupled with additional evidence regarding ulcer complications, co-prescribed PPIs are one of the recommended treatment options in current preventive clinical guidelines.[4–9, 17] However, despite these guidelines, gastroprotective co-therapies are often underprescribed or prescribed at inadequate doses by physicians even in at-risk patients[18–23] and, among those who do receive gastroprotection, adherence is suboptimal, resulting in poorer clinical outcomes.[21, 24, 25] Thus, beyond physician and patient education regarding the importance of adherence, there is a need for effective therapies to address the issue of NSAID-associated gastrointestinal (GI) toxicity in at-risk patients.

Combining PPI delivery with an NSAID in a single-tablet formulation may circumvent the issue of poor clinical outcomes associated with non-adherence. PN 400 (Patheon Pharmaceuticals Inc., Cincinnati, OH, USA on behalf of AstraZeneca, Wilmington, DE, USA and POZEN, Inc., Chapel Hill, NC, USA) is a fixed-dose combination formulation designed to provide sequential delivery of non-enteric-coated (EC), immediate-release (IR) esomeprazole 20 mg and EC naproxen (Patheon Pharmaceuticals Inc., Cincinnati, OH, USA) 500 mg in a single tablet.[26, 27] In these two phase 3 studies, treatment with PN 400 was compared with EC naproxen 500 mg alone over 6 months in at-risk patients to determine the incidence of cumulative endoscopic gastric ulcers and to evaluate safety and tolerability.

METHODS

These two identical, 6-month, randomized, double-blind, parallel-group, controlled, multicentre, phase 3 studies (PN400-301 and PN400-302; NCT00527787) were conducted in 59 (study 301) and 70 (study 302) centres in the United States between September 2007 and September 2008.

The primary objective was to determine if PN 400 reduces the risk of endoscopic gastric ulcers over the 6-month duration of the studies in at-risk patients compared with EC naproxen alone. Secondary objectives were to determine if PN 400 reduces the risk of duodenal ulcers, and to evaluate UGI symptoms and tolerability and safety profiles of PN 400 vs. EC naproxen. An additional objective was to evaluate the incidence of gastric ulcers in the subgroup of patients using LDA.

These studies were reviewed and approved by an independent ethics committee (New England Institutional Review Board) or individual study site review board, and all patients gave written, informed consent in accordance with the 1996 Declaration of Helsinki. The studies are registered at http://www.ClinicalTrials.gov (identifier: NCT00527787).

Patients

These studies included *Helicobacter pylori*-negative patients (as determined by a stool antigen test) with clinician-diagnosed osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or any other condition expected to require daily NSAID therapy for at least 6 months, who were either aged ≥50 years or aged 18–49 years with a documented history of uncomplicated gastric or duodenal ulcer within the past 5 years.

Patients with gastric or duodenal ulcer (≥3 mm diameter with depth) determined by endoscopy at baseline were excluded from these studies, as were patients with a history of hypersensitivity or allergy to any PPI or NSAID, and/or with any uncontrolled acute or chronic medical illness. Other exclusion criteria included prior GI disorders or surgery, and history of alcohol or drug abuse. The use of any other NSAID (other than LDA), anticoagulants or bisphosphonates during the treatment phase was disallowed, as was use of any PPI, H_2 receptor antagonist or sucralfate from within 2 weeks prior to baseline, and misoprostol from within 1 week prior to screening.

At screening visit 1, eligibility was established and patients provided informed consent. A physical examination and an electrocardiogram were also performed. Following a washout period of up to 14 days, during which disallowed medications were discontinued,

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eligible patients returned for a second screening visit and baseline endoscopy. Patients with no evidence of ulcer at baseline were randomized.

Study treatments

Patients were stratified by LDA use (≤325 mg) and randomized via the Interactive Voice Response System to receive either PN 400 or EC naproxen 500 mg alone, supplied as tablets of identical appearance in identical packaging to maintain blinding. The randomization schedule was provided by a third-party statistician. Patients, investigators and study staff remained blinded to treatment throughout the study. In the event of an emergency, an unblinding procedure was implemented.

Both PN 400 and EC naproxen 500 mg were taken orally, twice daily, 30–60 min before a meal in the morning and evening, for 6 months or until gastric ulcer was detected by endoscopy, at which point they were considered to have completed the study. Study drug was discontinued in the case of patient consent withdrawal, duodenal ulcer, pregnancy or any significant safety risk at the discretion of the investigator.

Acetaminophen (as per label dosing guidelines for osteoarthritis) and liquid antacid (up to 6 × 5 mL/day) were supplied for supplemental pain management and relief of UGI discomfort.

Study assessments

The prospectively defined primary efficacy endpoint was the cumulative incidence of gastric ulcers (≥3 mm diameter with depth) observed by endoscopy at 1, 3 and 6 months. To ensure an adequate sample size, a prespecified pooled analysis to assess the effect of LDA use (≤325 mg) on gastric ulcer incidence in these NSAID users was also conducted.

Prespecified secondary efficacy and tolerability endpoints included the cumulative, observed incidence of endoscopic duodenal ulcers at 1, 3 and 6 months, the incidence of predefined NSAID-associated UGI adverse events (AEs) including duodenal ulcers throughout the study (Appendix), the proportion of patients discontinuing treatment as a result of NSAID-associated UGI AEs, and the proportion of patients discontinuing as a result of any AE. Due to their clinical importance, duodenal ulcers were considered to be a study endpoint and, as such, were not recorded as AEs, but were included in the analysis of NSAID-associated UGI AE and AEs leading to study discontinuation.

The following patient-reported outcome questionnaires were also conducted: Severity of Dyspepsia Assessment (SODA), Overall Treatment Evaluation-Dyspepsia (OTE-DP) and assessment of heartburn. The SODA questionnaire, completed at baseline and months 1, 3 and 6, comprised 17 questions measuring three domains of dyspepsia: pain intensity, nonpain symptoms and satisfaction with dyspepsia-related health.[28, 29] Heartburn severity was also assessed at baseline and months 1, 3 and 6. The OTE-DP questionnaire is a derivative of the Global Ratings of Change questionnaire[30] and asked patients at month 6, 'Since treatment started, has there been any change in your abdominal pain and/or discomfort?' Responses were rated as 'better', 'worse' or 'same', and those patients reporting a difference since treatment started were asked to describe the degree of change and importance of the change.

Safety was assessed by the incidence of AEs, treatment-related AEs and serious AEs (SAEs), classified by the Medical Dictionary for Regulatory Activities (MedDRA) Version 10.1 and captured throughout the study via nondirective investigator questioning, patient reporting of symptoms, or through physical examinations, laboratory assessments and endoscopic findings. The following clinical laboratory tests were also performed: alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, blood urea nitrogen, creatinine and complete blood count at screening and/or baseline and at 1, 3 and 6 months.

Statistical analysis

The target sample size of 400 patients for each study, 200 per treatment arm, was based on the assumption that 15% of patients treated with naproxen would have a gastric ulcer over the 6-month study duration compared with 5% of patients treated with PN 400. A sample size of 200 patients per treatment group in each study has 90% power to detect a treatment difference of 10% with a two-sided significance level of 5% using Fisher's exact test.

All efficacy analyses were performed on the intent-to-treat (ITT) populations (all randomized patients who received ≥1 dose of study drug and had no ulcer as detected by endoscopy at screening). Planned supportive analyses were performed on the per-protocol population (patients in the ITT population with no major protocol violation and treatment compliance ≥70%). Subgroup analyses included use of LDA (yes/no), age (<60 years or ≥60 years) and history of ulcer within the past 5 years (yes/no).

A summary, including cumulative frequency, was produced for the observed incidence of gastric ulcers at 1, 3 and 6 months. The cumulative proportion of

patients developing gastric ulcers was analysed using a Cochran–Mantel–Haenszel (CMH) test stratified for LDA use. Time-to-event curves for the treatment groups were compared using a log-rank test stratified for LDA use. Kaplan–Meier estimates and corresponding 95% confidence intervals (CIs) for gastric ulceration were calculated for each treatment group at 1, 3 and 6 months. In a *post hoc* analysis, relative risk reduction (RRR) for PN 400 responders was calculated (RRR = [event rate in the control group − event rate in the treatment group]/ event rate in the control group).

Treatment group comparisons were performed using a CMH test stratified by LDA use for the following key secondary endpoints in a hierarchical testing sequence to control the overall alpha rate at a 0.05 level: the proportion of patients with prespecified NSAID-associated UGI AEs; the proportion of patients discontinuing as a result of prespecified UGI AEs; and the proportion of patients developing duodenal ulcers during 6 months of treatment. The proportion of patients discontinuing the study due to any AE or duodenal ulcer was analysed using a CMH test stratified by LDA use.

The mean change from baseline at 1, 3 and 6 months in the SODA scores was compared between treatment groups using an analysis of covariance model. The proportion of patients heartburn-free at 1, 3 and 6 months was analysed using a CMH test stratified by baseline heartburn severity and LDA use. The difference between treatment groups in distribution of responses on the OTE-DP was analysed using a modified Wilcoxon rank-sum test (Van Elteren).

Safety analyses were based on the safety population (all randomized patients who received ≥1 dose of study drug). AEs were summarized for each treatment group and evaluated for severity and causality of study drug. Changes in clinical laboratory values from baseline to follow-up were summarized at each visit using descriptive statistics.

RESULTS

Patients

Of 635 patients screened in study 301, 438 patients were randomized, 434 were treated and 333 completed (Figure 1a). In study 302, 639 patients were screened, 423 were randomized, 420 were treated and 304 completed (Figure 1b).

As seen in Table 1, approximately two-thirds of patients in the ITT populations of both studies were female. The mean age of patients was approximately 61 years in study 301 and 60 years in study 302. More than 80% of patients had osteoarthritis and approximately 23% used LDA at randomization. Baseline demographics and characteristics were similar between treatment groups in both studies, with the exception of the proportion of patients with rheumatoid arthritis, which was numerically higher in the PN 400 group compared with the EC naproxen group of study 301.

Assessment of ulcer incidence

In both studies, the cumulative observed incidence of gastric ulcers over 6 months was significantly lower in patients treated with PN 400 compared with those treated with EC naproxen (study 301: 4.1% vs. 23.1%, $P < 0.001$; study 302: 7.1% vs. 24.3%, $P < 0.001$). This translated to a RRR of 82.3% and 70.8% in studies 301 and 302, respectively. A significant difference was seen at month 1 and maintained throughout the study (Figure 2).

In a pooled analysis of both studies, the cumulative incidence of gastric ulcers was also significantly lower in the PN 400 group vs. the EC naproxen group in LDA users ($n = 201$) and in LDA non-users ($n = 653$) (Figure 3).

The cumulative incidence of duodenal ulcers was significantly lower in patients treated with PN 400 compared with those treated with EC naproxen (study 301: 0.5% vs. 5.1%, $P = 0.003$; study 302: 1.0% vs. 5.7%, $P = 0.007$). This represented a RRR of 90.1% and 82.4% in studies 301 and 302 respectively.

Tolerability

Predefined NSAID-associated UGI AEs. In the ITT population, the incidence of predefined NSAID-associated UGI AEs was significantly lower in the PN 400 treatment groups compared with the EC naproxen groups in both studies (study 301: 52.3% vs. 69.0%, $P < 0.001$; study 302: 54.3% vs. 71.9%, $P < 0.001$). The most common UGI AEs occurring in ≥10% of patients in either the PN 400 or EC naproxen treatment groups respectively of either study were erosive gastritis, gastritis, dyspepsia, and erosive duodenitis. A significantly lower proportion of patients discontinued due to UGI AEs (including duodenal ulcer) in the PN 400 groups compared with the EC naproxen groups (study 301: 3.2% vs. 12.0%, $P < 0.001$; study 302: 4.8% vs. 11.9%, $P = 0.009$).

Patient-reported outcomes. Patients treated with PN 400 reported significantly better UGI tolerability compared with those treated with EC naproxen in terms of SODA scores, proportion of heartburn-free patients (Table 2),

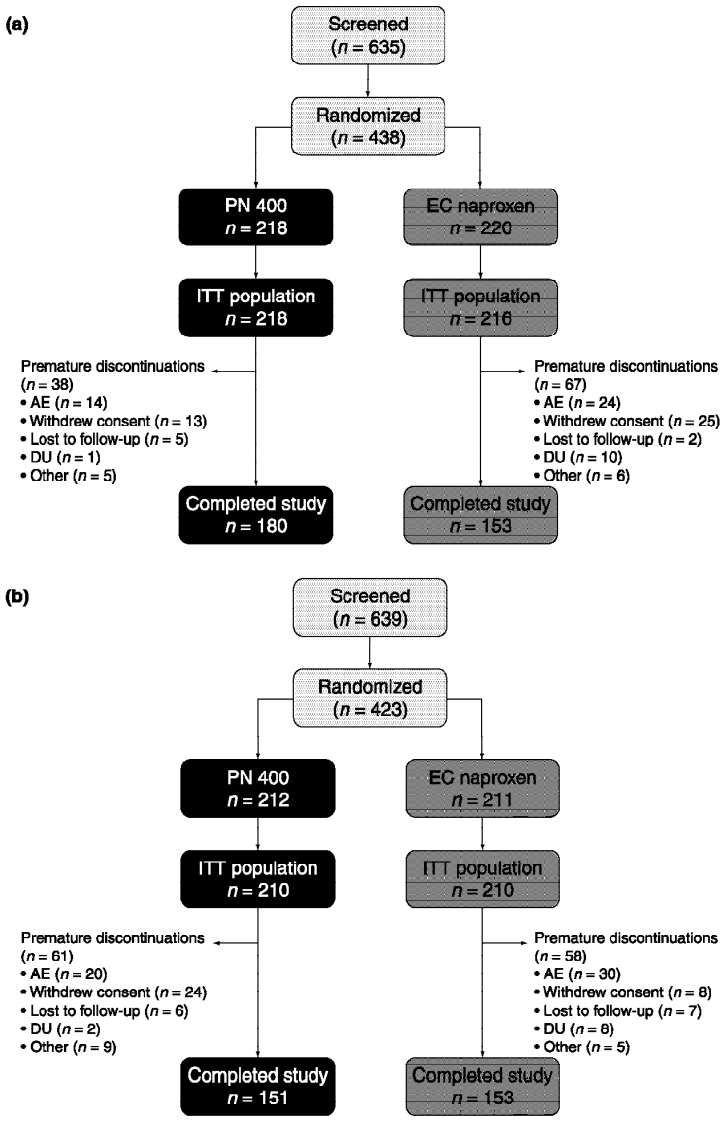

Figure 1 | Patient disposition in (a) study 301 and (b) study 302. Intent-to-treat (ITT) population: received ≥1 dose of study drug and had no ulcer at screening. Completed study: patients who completed 6 months of treatment or who discontinued due to gastric ulcer. EC, enteric-coated; ITT, intent-to-treat; AE, adverse event; DU, duodenal ulcer.

and OTE-DP response (Table 3) in both studies. In all three SODA domains (pain intensity, nonpain symptoms and satisfaction), PN 400 was associated with significantly greater improvements from baseline compared with EC naproxen. Based on a comparison of the distribution of primary OTE-DP responses (better, same or worse), PN 400 was associated with significantly greater improvement in upper abdominal pain and/or discomfort since treatment started relative to EC naproxen in study 301 ($P < 0.001$) and study 302 ($P = 0.017$).

Furthermore, of those patients who experienced an improvement in upper abdominal pain and/or discomfort, a numerically greater proportion treated with PN 400 reported that the degree of change was at least moderately better or more compared with EC naproxen (study 301: 86.0% vs. 69.2%; study 302: 79.8% vs. 61.9%). Conversely, of those patients who experienced a deterioration in symptoms, the proportion who reported the degree of change to be at least moderately worse or more was numerically similar or greater in the EC naproxen groups compared with the PN 400 groups (study 301: 60.0% vs. 61.1%; study 302: 74.3% vs. 62.5%). It is noteworthy that, regardless of blinded treatment group, approximately 80% of patients in both studies considered the change in OTE-DP to be important, specifically

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