

PN 400 Significantly Reduces the Incidence of Gastric Ulcers Compared with Enteric-Coated Naproxen in Patients Requiring Chronic NSAID Therapy Regardless of Low-Dose Aspirin Use: Results from Two Prospective, Randomized Controlled Trials

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Abstract

Introduction: Co-therapy with proton pump inhibitors reduces the risk of NSAID-associated ulcers but, in practice, adherence is often sub-optimal, leading to poor long-term clinical outcomes. Two Phase 3 studies evaluated the upper gastrointestinal (UGI) efficacy and safety of PN 400, a fixed-dose combination tablet designed to provide sequential delivery of immediate-release (IR) esomeprazole (20 mg) and enteric-coated (EC) naproxen (500 mg), compared with EC naproxen (500 mg) alone in at-risk patients.

Methods: Two randomized, double-blind, controlled, multicenter studies enrolled *H. pylori*-negative patients with OA, RA, or any other condition requiring chronic NSAID therapy at risk of ulcers (age ≥ 50 yrs or 18-49 yrs with a history of gastric ulcer [GU] or duodenal ulcer [DU] within the past 5 yrs). Patients were randomized to PN 400 BID or EC naproxen 500 mg BID for 6 months. The primary endpoint was the cumulative incidence of GUs (≥ 3 mm diameter with depth) observed by endoscopy at 1, 3, and 6 months. A planned pooled analysis to assess the effect of low-dose aspirin use (LDA ≤ 325 mg) on GU incidence, and an analysis of pre-specified NSAID-associated UGI AEs (including DU) were also conducted.

Results: Study A: 438 patients were randomized, 434 were treated; Study B: 423 patients were randomized, 420 were treated. Baseline demographics were similar between groups in both studies. Approximately 82% of patients had OA and 6% had RA. In both studies, the incidence of GUs over 6 months was significantly lower in the PN 400 groups vs the EC naproxen groups (Table). The pooled incidence of GUs was significantly lower in the PN 400 group vs the EC naproxen group in LDA 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 previously described pre-specified secondary endpoint was significantly lower in the PN 400 groups (Table).

	Study A		p	Study B		p
	PN 400 (n=218)	EC naproxen (n=216)		PN 400 (n=210)	EC naproxen (n=210)	
GU, n (%)	9 (4.1)	50 (23.1)	<0.001	15 (7.1)	51 (24.3)	<0.001
DU, n (%)	1 (0.5)	11 (5.1)	0.003	2 (1.0)	12 (5.7)	0.007
UGI AE/DU, n (%)	114 (52.3)	149 (69.0)	<0.001	114 (54.3)	151 (71.9)	<0.001

Conclusion: PN 400 significantly reduces the incidence of GUs, regardless of concomitant LDA use, and DUs in at-risk patients. PN 400, a fixed-dose combination of EC naproxen 500 mg and IR esomeprazole 20 mg, provides built-in gastroprotection and offers a treatment option for decreasing NSAID-ulcer occurrence in an appropriate target patient population.

Introduction

- ▶ Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the signs and symptoms of arthritis, but their use is associated with an increased risk of upper gastrointestinal (UGI) adverse events (AEs), including non-ulcer dyspepsia, symptomatic and asymptomatic ulcers as well as complicated ulcers.¹
- ▶ Co-therapy with proton pump inhibitors (PPIs) is recommended to reduce the risk of NSAID-associated ulcers² but, in practice, patient adherence is often sub-optimal, leading to poorer long-term clinical outcomes.³
- ▶ PN 400 is a fixed-dose combination designed to provide sequential delivery of immediate-release (IR) esomeprazole (20 mg) and enteric-coated (EC) naproxen (500 mg) in a single tablet.^{4,5}
- ▶ The objective of these two studies was to demonstrate that PN 400 is effective in reducing the risk of gastric ulcers (GUs) in patients at risk of developing NSAID-associated ulcers.

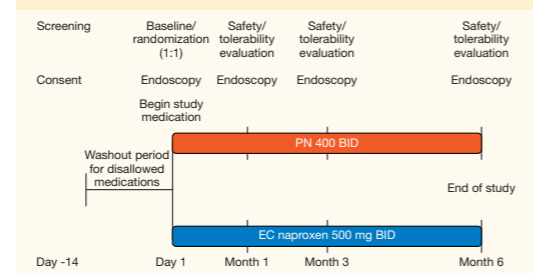
Methods

Study design

- ▶ Two identical, randomized, double-blind, controlled, multicenter Phase 3 trials conducted in the U.S. between September 2007 and September 2008.
- ▶ All patients provided written, informed consent and study approval was obtained from a central or local Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.
- ▶ Eligible patients were randomized to receive either PN 400 or EC naproxen (500 mg) alone. Randomization was stratified by use of low-dose aspirin (LDA).

- ▶ Patients received study treatment twice daily (30-60 minutes before a meal in the morning and evening) for 6 months or until an ulcer had been confirmed by scheduled endoscopy (Figure 1).
- ▶ Scheduled endoscopies were performed at baseline, and at 1, 3, and 6 months.

Figure 1. Study design



Patients

- ▶ Both studies included patients 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 aged ≥ 50 years or 18-49 years with a documented history of an uncomplicated GU or duodenal ulcer (DU) within the past 5 years, and were *H. pylori*-negative as determined by a stool antigen test at baseline.
- ▶ Patients with either a GU or DU (≥ 3 mm diameter with depth) determined by endoscopy at baseline were excluded from these studies.
- ▶ Concomitant use of any other NSAID or gastroprotective agent (histamine receptor antagonists, PPIs, or misoprostol) was disallowed. Other concomitant medication not permitted during the study included anticoagulants, antiplatelet agents used concomitantly with aspirin, oral bisphosphonates, and sucralfate.
- ▶ Use of low-dose aspirin (≤ 325 mg daily) was allowed.

Primary and secondary endpoints

- ▶ The primary efficacy endpoint was the cumulative incidence of GUs (≥ 3 mm diameter with depth) observed by endoscopy during 6 months of treatment.
 - A pre-planned pooled analysis of both studies was also conducted to assess the effect of LDA on the incidence of GUs.
- ▶ Secondary efficacy and tolerability endpoints included:
 - Cumulative incidence of DUs over 6 months.
 - Incidence of pre-specified, NSAID-associated UGI AEs, including DUs.
 - Proportion of patients discontinuing treatment as a result of pre-specified, NSAID-associated UGI AEs, including DUs.
 - Proportion of patients discontinuing treatment as a result of any AE, including DUs.
- ▶ Safety assessment endpoints included the overall incidence of AEs and serious AEs (SAEs).
- ▶ Data on patient-reported outcomes from these studies will be reported at the 2009 American College of Gastroenterology Annual Scientific Meeting.⁶

Statistical analysis

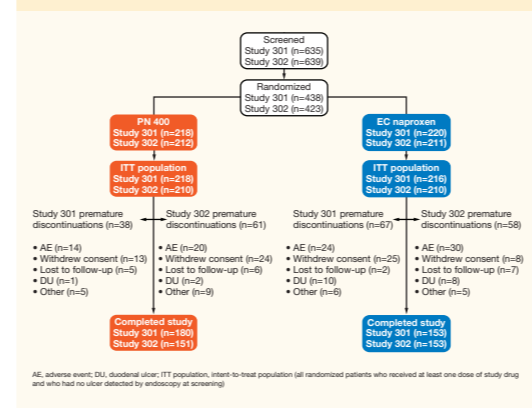
- ▶ The cumulative proportion of patients developing GUs was analyzed using a Cochran-Mantel-Haenszel test stratified by LDA use. This test was also used to perform treatment-group comparisons for the cumulative proportion of patients developing DUs, and the proportion of patients with, and discontinuing as a result of, NSAID-associated UGI AEs/DUs.

Results

Patients

- ▶ In Study 301, 438 patients were randomized and 333 completed. In Study 302, 423 patients were randomized and 304 completed (Figure 2).

Figure 2. Study disposition



- ▶ Baseline demographics and disease characteristics were similar between treatment groups in both studies (Table 1).

Table 1. Baseline patient demographics and disease characteristics

	Study 301		Study 302	
	PN 400 (n=218)	EC naproxen (n=216)	PN 400 (n=210)	EC naproxen (n=210)
Sex, n (%)				
Female	150 (68.8)	149 (69.0)	132 (62.9)	142 (67.6)
Race, n (%)				
White	184 (84.4)	181 (83.8)	183 (87.1)	190 (90.5)
Black	27 (12.4)	32 (14.8)	26 (12.4)	17 (8.1)
Other	7 (3.2)	3 (1.4)	1 (0.5)	3 (1.4)
Age, years				
Mean	60.8	61.9	59.6	59.4
Range	30-90	43-90	27-85	29-82
LDA use at randomization, n (%)	53 (24.3)	51 (23.6)	46 (21.9)	51 (24.3)
Ulcer history within previous 5 years, n (%)	15 (6.9)	13 (6.0)	18 (8.6)	23 (11.0)
Indication for NSAID use, n (%)				
Osteoarthritis	172 (78.9)	186 (86.1)	173 (82.4)	166 (79.0)
Rheumatoid arthritis	22 (10.1)	8 (3.7)	11 (5.2)	9 (4.3)
Other	53 (24.3)	38 (17.6)	48 (22.9)	59 (28.1)

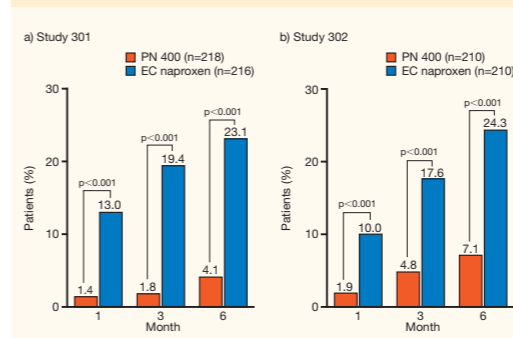
LDA, low-dose aspirin; NSAID, nonsteroidal anti-inflammatory drug

- ▶ The majority of patients in both studies had osteoarthritis. In Study 301, a higher proportion of patients had rheumatoid arthritis in the PN 400 treatment group compared with the EC naproxen group (10.1% vs 3.7%, respectively).
- ▶ The proportion of patients with a history of ulcer in the previous 5 years was low, but slightly higher in Study 302 than in Study 301 (9.8% vs 6.5%, respectively).

Efficacy

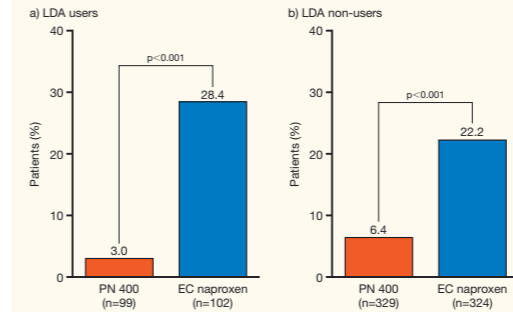
- ▶ In both studies, the cumulative observed incidence of GUs over 6 months was significantly lower in patients treated with PN 400 compared with those treated with EC naproxen (Figure 3). Significant separation between treatment groups was observed as early as 1 month and was maintained throughout 6 months of therapy.

Figure 3. Cumulative incidence of GUs (≥ 3 mm) over 1, 3, and 6 months: PN 400 vs EC naproxen



- ▶ The pooled observed incidence of GUs was significantly lower in the PN 400 group compared with the EC naproxen group, regardless of LDA use (Figure 4).

Figure 4. Pooled analysis of the cumulative incidence of GUs (≥ 3 mm) over 6 months in LDA users and non-users: PN 400 vs EC naproxen



- ▶ The cumulative incidence of DUs over 6 months was also significantly lower in the PN 400 treatment groups compared with the EC naproxen groups in both studies (Table 2).

Table 2. Incidence of DUs and pre-specified, NSAID-associated UGI AEs including DUs over 6 months

	Study 301		p	Study 302		p
	PN 400 (n=218)	EC naproxen (n=216)		PN 400 (n=210)	EC naproxen (n=210)	
DU, n (%)†	1 (0.5)	11 (5.1)	0.003	2 (1.0)	12 (5.7)	0.007
UGI AE/DU, n (%)	114 (52.3)	149 (69.0)	<0.001	114 (54.3)	151 (71.9)	<0.001
Discontinuations due to UGI AE/DU, n (%)	7 (3.2)	26 (12.0)	<0.001	10 (4.8)	25 (11.9)	0.009

†Cumulative incidence of DUs over 6 months
NSAID, nonsteroidal anti-inflammatory drug; DU, duodenal ulcer; UGI, upper gastrointestinal; AE, adverse event

Safety and Tolerability

- ▶ In both studies, the overall incidence of AEs was similar in the PN 400 treatment groups compared with the EC naproxen groups (Study 301: 78.0% vs 81.5%; Study 302: 76.2% vs 82.9%).
- ▶ The most commonly reported AEs in both studies were erosive gastritis, gastritis, and dyspepsia (Table 3).

Table 3. Most commonly reported treatment-emergent adverse events ($\geq 10\%$ of patients in either treatment group from either study)

Adverse event	Patients, n (%)			
	Study 301		Study 302	
	PN 400 (n=218)	EC naproxen (n=216)	PN 400 (n=210)	EC naproxen (n=210)
Erosive gastritis	45 (20.6)	81 (37.5)	38 (18.1)	81 (38.6)
Gastritis	39 (17.9)	28 (13.0)	34 (16.2)	32 (15.2)
Dyspepsia	36 (16.5)	65 (30.1)	41 (19.5)	49 (23.3)
Erosive duodenitis	4 (1.8)	30 (13.9)	5 (2.4)	20 (9.5)

- ▶ There were no deaths in either study. Treatment-related SAEs were DU hemorrhage (n=1) and non-cardiac chest pain (n=1), both in the EC naproxen group of Study 301.
- ▶ Significantly fewer patients treated with PN 400 discontinued as a result of any AE compared with those treated with EC naproxen (Study 301: 6.9% vs 15.7%, $p = 0.004$; Study 302: 10.5% vs 18.1%, $p = 0.029$).
- ▶ Significantly fewer patients treated with PN 400 discontinued due to pre-specified UGI AEs, including DUs, compared with those treated with EC naproxen (Table 2).
- ▶ The incidence of pre-specified, NSAID-associated UGI AEs including DUs were significantly lower in the PN 400 treatment groups compared with the EC naproxen groups in both studies (Table 2).

Summary

- ▶ PN 400 significantly reduces the incidence of GUs (regardless of concomitant LDA use) compared with EC naproxen in patients requiring NSAID therapy.
- ▶ PN 400 also significantly reduces the incidence of DUs compared with EC naproxen in the overall or in the ITT patient population.
- ▶ Compared with EC naproxen, PN 400 had a lower rate of UGI AEs/DUs and a lower rate of associated discontinuations.

Conclusions

- ▶ There is a need for novel strategies to facilitate improved adherence to existing therapies for patients taking chronic NSAID therapy.
- ▶ The PN 400 formulation provides built-in gastroprotection with every dose of naproxen and may be an effective treatment option for patients at risk of developing NSAID-associated ulcers.

Disclosure

This study was sponsored by POZEN Inc. Medical writing support was provided by Lynsey Stevenson at Complete Medical Communications on behalf of AstraZeneca. Dr J.L. Goldstein is a consultant to both POZEN and AstraZeneca and has received honoraria, travel expenses, educational grants, and research grants from both companies. Dr M. Hochberg is a consultant to both POZEN and AstraZeneca.

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