

# A novel, single-tablet formulation that delivers immediate-release omeprazole followed by enteric-coated (EC) naproxen significantly reduces the incidence of gastric ulcers compared with EC naproxen alone: results of a prospective, randomised, double-blind, 6-month study including patients with OA and RA

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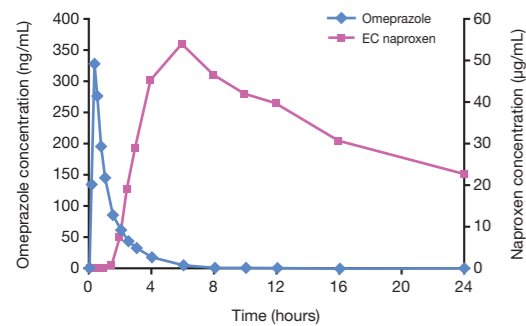
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## Introduction

- Upper gastrointestinal (GI) complications associated with non-steroidal anti-inflammatory drug (NSAID) therapy are a significant cause of morbidity and mortality and are associated with decreased persistence.<sup>1</sup>
- The efficacy of proton-pump inhibitors (PPIs) for the prevention of mucosal injury, endoscopic ulcers and upper GI symptoms associated with NSAID therapy, is well documented.<sup>2,3</sup>
- Non-adherence to concomitant PPI therapy is associated with decreased relative effectiveness of preventing upper GI bleeding events.<sup>4</sup> Persistence of concomitant PPI therapy is often low;<sup>5</sup> hence, novel therapeutic approaches would be beneficial to reduce the incidence of upper GI events in patients requiring chronic NSAID therapy.
- A single-tablet formulation of a non-enteric-coated PPI and an enteric-coated (EC) NSAID could address the issue of non-adherence. PN200 provides sequential delivery of omeprazole 20 mg + EC naproxen 500 mg. The PN200 formulation delivers omeprazole before absorption of EC naproxen (Figure 1).

Figure 1. Pharmacokinetic profile of PN200



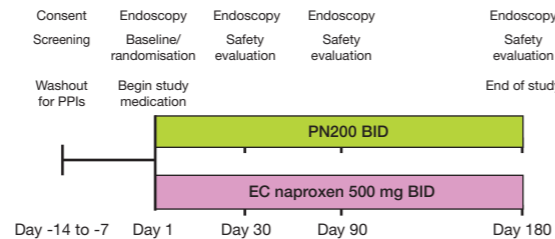
First-dose kinetics from Study PN200-301; a single-dose crossover pharmacokinetic study, n=30 (POZEN: data on file)

- The objectives of this study were to compare the safety and tolerability of PN200 with EC naproxen 500 mg alone.

## Methods

- The protocols were reviewed and approved by an independent ethics committee and all subjects gave written, informed consent.
- Study PN200-301 was a 6-month, randomised, double-blind, parallel-group, multicentre study in patients with arthritis requiring chronic NSAID treatment. Patients were randomised to either PN200 BID or EC naproxen 500 mg BID (Figure 2).

Figure 2. Study design



- Patients were seronegative for *H.pylori* and were at risk of NSAID-associated gastric ulcers (aged 18-49 years with a history of gastric ulcer or duodenal ulcer within the past 5 years, or aged  $\geq 50$  years).
- Major exclusion criteria included use of antisecretory agents or misoprostol within 14 days prior to the baseline endoscopy (esophagogastroduodenoscopy [EGD]); and any gastric ulcer or duodenal ulcer ( $\geq 3$  mm diameter with depth) at baseline EGD.
- EGD was performed at baseline and 1, 3 and 6 months.
- Safety evaluations were performed at 1, 3 and 6 months.

## Endpoints

- The primary endpoint was the incidence of gastric ulcer ( $\geq 3$  mm diameter with depth) during the study estimated by survival analysis.
- Secondary endpoints included the incidence of duodenal ulcers.

## Results

- Study disposition is shown in Figure 3 and patient demographics are shown in Table 1.
- 290 patients completed the 6-month study: PN200 BID (n=155 [75.2%]) and EC naproxen 500 mg BID (n=135 [66.5%]).
- The incidence of gastric ulcers during the course of the study was significantly lower in the PN200 group compared with the EC naproxen group (8.3% vs 29.4% for PN200 and EC naproxen, respectively; relative risk [RR] of 72%,  $p < 0.001$ ) (Figure 4).
- The reduction in the incidence of gastric ulcers associated with PN200 in comparison with EC naproxen was similar in patients taking low-dose aspirin ( $\geq 325$  mg) compared with patients not taking low-dose aspirin (Figure 5).
- The incidence of duodenal ulcers was significantly lower in patients receiving PN200 BID compared with patients receiving EC naproxen 500 mg BID (Figure 6).

Figure 3. Study disposition

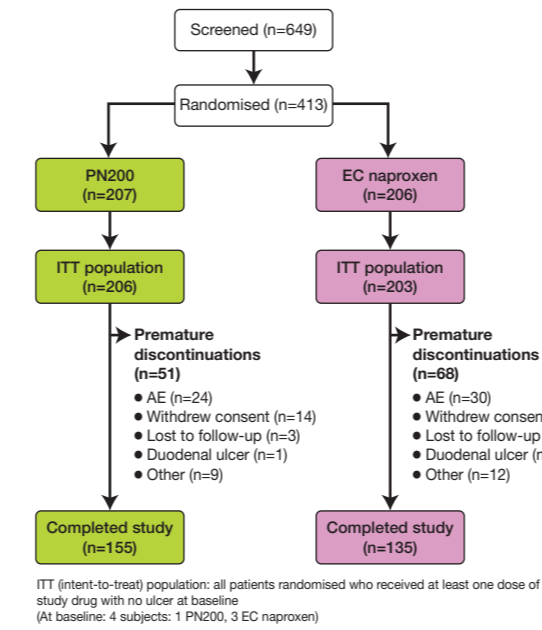


Table 1. Patient demographics (ITT population)

|                             |                        | PN200 BID<br>n=206 | EC naproxen<br>500 mg BID<br>n=203 |
|-----------------------------|------------------------|--------------------|------------------------------------|
| Gender, n (%)               | Male                   | 73 (35)            | 60 (30)                            |
|                             | Female                 | 133 (65)           | 143 (70)                           |
|                             |                        |                    |                                    |
| Race, n (%)                 | White                  | 175 (85)           | 173 (85)                           |
|                             | Black                  | 24 (12)            | 20 (10)                            |
|                             | Other                  | 7 (3)              | 10 (5)                             |
| Age                         | Mean                   | 61                 | 61                                 |
|                             | $\geq 50$ years, n (%) | 106 (51)           | 100 (49)                           |
| Aspirin use                 | <60 years, n (%)       | 199 (97)           | 201 (99)                           |
|                             | $\geq 50$ years, n (%) | 56 (27)            | 52 (26)                            |
| Ulcer Hx, n (%)             | Gastric                | 13 (6)             | 4 (2)                              |
|                             | Duodenal               | 2 (1)              | 0                                  |
| Indication NSAID use, n (%) | Osteoarthritis         | 168 (82)           | 169 (83)                           |
|                             | Rheumatoid arthritis   | 8 (4)              | 14 (7)                             |
|                             | Ankylosing spondylitis | 1 (0.5)            | 0                                  |
|                             | Other*                 | 36 (18)            | 25 (12)                            |

\*Other includes: back pain; back pain-herniated disc surgery; chronic back pain; chronic dental pain; chronic headache; chronic knee pain; chronic lower back pain; chronic plantar fasciitis; chronic spondylitis; degenerative arthritis; degenerative disc disease; DeQuervain's tenosynovitis; fibromyalgia; herniated discs; hip fracture; inflammatory arthritis; left Achilles calcific insertional peritendinitis; leg pain; low back pain; neck, shoulder, bilateral hand pain; pain in bilateral hips; psoriatic arthritis; shoulder pain; spinal stenosis

Figure 4. Survival analysis of incidence of gastric ulcers over time

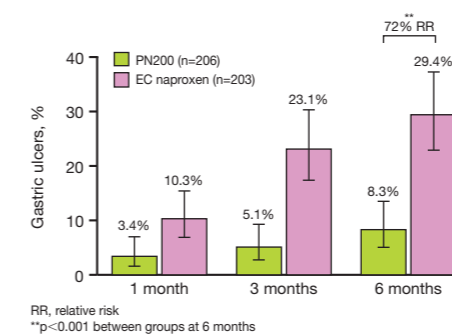


Figure 5. Cumulative incidence of gastric ulcers over 6 months: ASA vs no ASA

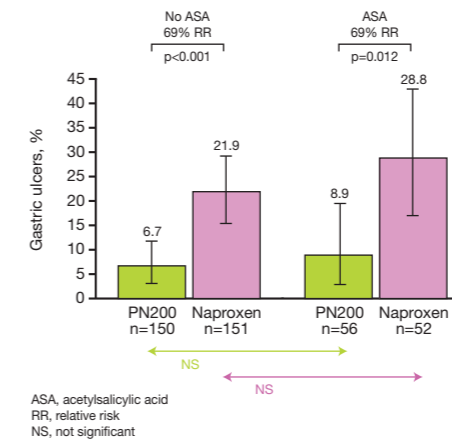
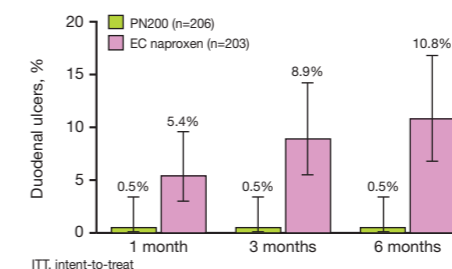


Figure 6. Survival analysis of incidence of duodenal ulcers over 6 months (ITT)



- There were significantly fewer upper GI adverse events in patients receiving PN200 BID compared with patients receiving EC naproxen 500 mg BID, and fewer premature discontinuations due to upper GI adverse events (Table 2).

Table 2. Treatment-emergent adverse events; n (%)

|  | PN200 BID<br>n=206 | EC naproxen<br>500 mg BID<br>n=203 | p      |
|--|--------------------|------------------------------------|--------|
| Any upper GI AE                        | 105 (51.0)         | 144 (70.9)                         | <0.001 |
| Any upper GI AE related to study drug  | 86 (41.7)          | 133 (65.5)                         | <0.001 |
| Dyspeptic symptoms*                    | 17 (8.3)           | 18 (8.9)                           | NS     |
| Use of antacid rescue medication       | 145 (70.4)         | 170 (83.7)                         | 0.001  |
| Upper GI AE leading to discontinuation | 9 (4.4)            | 22 (10.8)                          | 0.012  |

GI, gastrointestinal; AE, adverse event; NS, not significant  
\*upper abdominal pain, dyspepsia, eructation, gastric discomfort

## Conclusions

- Compared with EC naproxen, PN200 was associated with a significantly lower incidence of both gastric ulcers and duodenal ulcers.
- Concomitant low-dose aspirin therapy had no significant effect on the observed gastric ulcer risk reduction seen with PN200.
- The PN formulation may offer a potential treatment option for patients at risk of NSAID-associated gastric ulcers or duodenal ulcers and may help address issues of persistence of use and compliance with gastroprotective agents.

## References

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