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Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, Phase I study in healthy volunteers

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SUMMARY

Background
PN 400 is a fixed-dose combination formulated to provide sequential delivery of immediate-release (IR) esomeprazole and enteric-coated (EC) naproxen.

Aim
To evaluate gastric acid suppression with three doses of esomeprazole in PN 400 compared with EC esomeprazole 20 mg.

Methods
In this Phase I, randomized, open-label study, 28 healthy adults received PN 400 b.d. (naproxen 500 mg plus esomeprazole 10, 20 and 30 mg) and non-EC naproxen 500 mg b.d. plus EC esomeprazole 20 mg o.d., each for 9 days in a crossover fashion. The primary endpoint was percentage of time on day 9 that intragastric pH was >4.0; secondary endpoints included pharmacokinetics and safety.

Results
Day 9 percentage of time where intragastric pH was >4.0 was 76.5%, 71.4%, 40.9% and 59.9% for PN 400 containing 30, 20 and 10 mg esomeprazole, and naproxen plus esomeprazole 20 mg respectively. This was significantly greater for PN 400 containing 30 and 20 mg esomeprazole vs. naproxen plus esomeprazole 20 mg (95% CI: 13.0–26.0 and 7.8–20.7 respectively). The pharmacokinetics of PN 400 were consistent with its formulation. No serious adverse events occurred.

Conclusion
PN 400 containing 20 mg esomeprazole was the lowest dose to achieve gastric acid suppression comparable to EC esomeprazole 20 mg and was selected for further evaluation.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide, used by more than 30 million people every day.[1] However, they are associated with a substantial risk of upper gastrointestinal adverse events, ranging from ulcers to serious ulcer complications such as perforation, obstruction and bleeding.[2]

Treatment guidelines generally recommend that patients requiring chronic NSAID therapy who have risk factors for gastrointestinal ulcer complications (e.g. advanced age, a history of gastroduodenal ulcers or concomitant use of corticosteroids, aspirin and/or anticoagulants[3, 4]) should be treated with cyclo-oxygenase-2 selective NSAIDs or traditional, nonselective NSAIDs plus gastroprotective co-therapy. In particular, enteric-coated (EC) proton pump inhibitors have well-documented efficacy for reducing the incidence of NSAID-associated endoscopic ulcers and upper gastrointestinal symptoms,[5, 6] and are recognized as an effective gastroprotective strategy for at-risk patients.[4]

However, despite clinical guidelines, evidence from practice suggests that gastroprotective co-therapy strategies are underutilized by physicians[7] and poorly adhered to by patients.[8–11] Partly as a result of this, there has been growing interest in the use of fixed-dose combination therapies of NSAIDs with gastroprotective agents in a single tablet to, among other potential benefits, improve patient adherence.

PN 400 (VIMOVO; AstraZeneca, Wilmington, DE, USA and POZEN, Inc., Chapel Hill, NC, USA) is a fixed-dose combination of EC naproxen 500 mg and immediate-release (IR) esomeprazole 20 mg that is in development for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk for developing NSAID-associated gastric ulcers. Naproxen is a nonselective NSAID with a well-established efficacy and safety profile[12–14] and esomeprazole is a proton pump inhibitor with effective gastric acid suppression[15] that, when administered as an EC preparation, has demonstrated clinical efficacy to reduce the occurrence of endoscopic gastric and duodenal ulcers in at-risk patients using NSAIDs.[16] The PN 400 single-tablet formulation comprising an EC naproxen core surrounded by an IR esomeprazole mantle has been designed to provide sequential delivery of gastroprotective esomeprazole before systemic exposure to naproxen.

In this study, the pharmacokinetics, pharmacodynamics and safety of three different dose formulations of PN 400 were evaluated and compared with naproxen 500 mg and EC esomeprazole 20 mg, with the aim of determining levels and time to exposure for these drugs, and determining the dose of IR esomeprazole in PN 400 to provide gastric acid suppression similar to EC esomeprazole.

MATERIALS AND METHODS

Study design

This was a prospective, randomized, Phase I, open-label, single-centre, cross-over study comprising four treatment periods that was conducted in the US between 3 April and 25 June 2007.

On day 1 of the first treatment period, study participants were randomized into one of four treatment sequences to receive each of four treatments for 9 days in a crossover fashion. There was a washout period of ≥12 days between treatments (Table 1). Study medication was administered orally with 240 mL of water 60 min before standardized meals in the morning and evening. All study medication was administered at the study site by staff, with a mouth check performed to ensure treatment compliance.

Participants were randomized into treatment sequences according to their unique treatment number, which was assigned consecutively from a randomization schedule provided by POZEN following completion of screening.

The study was reviewed and approved by an Investigational Review Board at the study site and all participants gave written, informed consent in accordance with the 1996 Declaration of Helsinki.

Table 1 | Study treatment

Treatment	Study medication
PN 400/E30	EC naproxen 500 mg/IR esomeprazole 30 mg b.d.
PN 400/E20	EC naproxen 500 mg/IR esomeprazole 20 mg b.d.
PN 400/E10	EC naproxen 500 mg/IR esomeprazole 10 mg b.d.
Naproxen + EC E20	Non-EC naproxen* 500 mg b.d. and EC esomeprazole 20 mg o.d.

b.d., twice daily; EC, enteric coated; IR, immediate release; o.d., once daily.

*Non-EC naproxen was inadvertently used as a control instead of EC naproxen.

Participants

Eligible participants were healthy adults aged 18–55 years who tested negative for *Helicobacter pylori* infection and had no history of peptic ulcer disease or other acid-related gastrointestinal symptoms. Participants with a history of hypersensitivity, allergy or intolerance to any NSAID or proton pump inhibitor were excluded from the study. Other exclusion criteria included the presence of any uncontrolled acute or chronic illness, any gastrointestinal disorder causing impaired drug absorption and a history of alcohol or drug abuse.

The ingestion of grapefruit juice was disallowed within 10 days of first dose and throughout the study. The use of any concomitant medications was not permitted unless approved by the principal investigator. Specifically, the use of any proton pump inhibitor or gastroprotective agent, any misoprostol-containing product, sucralfate, antibiotics, antacid or Pepto-Bismol (Procter & Gamble, Cincinnati, OH, USA) was disallowed within 14 days prior to dosing and throughout the study. Additionally, within 7 days prior to dosing and throughout the study, the use of any NSAID, bisphosphonate, steroid, anticoagulant, anticholinergic or monoamine oxidase inhibitor was also disallowed.

During a screening period of up to 14 days, participants were assessed for eligibility; a physical exam and 12-lead electrocardiogram were performed; vital signs were recorded and clinical laboratory samples were taken. Participants returned on day 0, when eligibility and vital signs were reviewed again and those who continued to meet eligibility criteria remained at the study site to enter the treatment phase.

Study endpoints

The primary pharmacodynamic endpoint was the percentage of time over 24 h on day 9 of each treatment phase that intragastric pH was >4.0. The percentage of time over 24 h on day 1 that intragastric pH was >4.0 was assessed as a secondary endpoint. The percentage of time that intragastric pH was >3.0 and >5.0 on days 1 and 9 was also assessed.

Intragastric pH was measured by a pH probe (Digitrapper pH data logger; Medtronics, Minneapolis, MN, USA) placed prior to administration of study medication on day 1, with the distal electrode 10 cm below the lower oesophageal sphincter and the proximal electrode 5 cm above. The pH probe was removed in the morning of day 2 prior to morning (AM) dosing. This was repeated on day 9, with the probe removed on day 10. Collected pH data were evaluated by a third party blinded to study treatment.

On days 1 and 9 of each treatment period, pre-AM dose and serial post-AM dose blood samples were collected for pharmacokinetic (PK) assessments. Final blood samples were collected predose in the morning of day 2 and following completion of treatment on day 10.

The following PK parameters for esomeprazole and naproxen were calculated for each treatment after the AM and afternoon (PM) doses: peak plasma concentration ($C_{max,AM}$ and $C_{max,PM}$), time to peak plasma concentration ($t_{max,AM}$ and ($t_{max,PM}$), area under the plasma concentration vs. time curve from time zero to the last time point with measurable drug concentration ($AUC_{0-t,AM}$ and $AUC_{0-t,PM}$) and half-life ($t_{½}$). *AUC* from time zero (time of dosing) to 10 h post-AM dose ($AUC_{0-10,AM}$), *AUC* from time zero to 14 h post-PM dose ($AUC_{0-14,PM}$) and a total daily *AUC* (AUC_{0-24}) were also calculated.

Safety for each treatment was assessed by the incidence of adverse events, a physical examination, vital signs and the following clinical laboratory tests: creatinine, alanine aminotransferase, aspartate aminotransferase, haematocrit, alkaline phosphatase, bilirubin, blood urea nitrogen, complete blood count and complete urinalysis.

Adverse events were recorded from the start of treatment until the final visit and were assessed for severity and relationship to study drug. Clinical laboratory tests, physical examination and measurement of vital signs were performed at screening and the final visit (on completion of the fourth treatment period or discontinuation). Vital signs were also measured in the PM of all days 0 and 8 visits, and complete blood count (without differential) was repeated on day 8 of the first three treatment periods and day 0 of the fourth period.

Statistical analysis

This study planned to enrol 28 subjects with the goal of having 24 evaluable subjects for analysis. A total of 24 subjects provided 80% power to reject the null hypothesis that the difference between each of the PN 400 treatments and the active control treatment in percentage of time that pH was >4.0 over 24 h was ≤−8% using a pairwise *t*-test with a one-sided significance level of 0.05.

All statistical analyses were completed using the SAS system, version 8.2 or higher (SAS Institute Inc., Cary, NC, USA). The intent-to-treat (ITT) population was defined as all randomized participants who had valid pH data for at least one treatment period (received all doses of study medication during that treatment period, had at least 20 h of valid pH data determined by the clinical investigator, did not have technical failures of the pH

recording and did not have ≥1 continuous hour with pH data outside the reference range). Primary pharmacodynamic analyses were based on the per protocol population (participants in the ITT population who had valid pH data for all four treatment periods and did not violate the protocol in any major way that would have impacted the evaluation of pharmacodynamic endpoints). The percentage of time that pH was >4.0 on days 1 and 9 was summarized by treatment and analysed by analysis of variance. The least squares (LS) means for each treatment, the difference of LS means between each of the PN 400 treatments and the active control and 95% confidence intervals (CIs) for all treatment differences were calculated.

Pharmacokinetic analyses were performed on the PK population (all randomized participants who received all doses of study medication for at least one treatment period and had adequate blood sampling to determine the PK parameters of the study drugs).

Plasma esomeprazole and naproxen concentration data were summarized by treatment and study day at each sampling time using descriptive statistics including mean, standard deviation, % coefficient of variance, median, minimum and maximum. Geometric mean and associated 95% CIs were also calculated for all PK parameters, except t_{max}. Plasma concentrations below the lower limit of quantification were treated as a zero value for calculating descriptive statistics. The mean/median value at a time point with ≥1 value below the lower limit of quantification was reported unless the mean/median value was below the lower limit of quantification of the assay, in which case, the value was reported as below the lower limit of quantification.

The plasma concentration vs. time data of each analyte were subjected to noncompartmental analysis using WinNonlin version 4.1 (Pharsight Corporation, Mountain View, CA, USA). Statistical analysis was performed using analysis of variance to determine the point estimate and associated 90% CI of the days 9 to 1 ratios for the following parameters: $C_{max,AM}$, $C_{max,PM}$, $AUC_{0-10,AM}$, $AUC_{0-14,PM}$ and AUC_{0-24}. Natural log-transformed C_{max} and AUC values were used for the analyses, thus geometric LS mean ratios for each parameter were determined.

Safety analyses were based on the safety population (all subjects who received at least one dose of study medication). Adverse events were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA, version 8.0). Vital signs and clinical laboratory test results were summarized by visit.

RESULTS

Participants

Twenty-eight participants were randomized to treatment and 27 completed the study (Figure 1). A majority of participants were male (68%) and all were white. Mean age was 24.9 years. Demographics and baseline characteristics of enrolled participants are shown in Table 2.

Pharmacodynamics

On day 9, the mean percentage of time where intragastric pH was >4.0 over 24 h was 76.5%, 71.4%, 40.9% and 59.9% for PN 400/E30, PN 400/E20, PN 400/E10 and naproxen + EC E20 respectively (Table 3). Compared with naproxen + EC E20 treatment, this percentage was significantly greater for PN 400/E30 and PN 400/E20 (95% CI: 13.0–26.0 and 7.8–20.7 respectively), but was significantly less for treatment with PN 400/E10 (95% CI: −22.3 to 9.7). Treatment with PN 400/E10 also resulted in the greatest variability of all treatments, as indicated by the high co-efficient of variation (Table 3).

Compared with observations on day 9, the mean percentage of time with intragastric pH >4.0 over 24 h was lower on day 1 for all treatment groups (27.8%, 20.5%, 12.8% and 21.3% for PN 400/E30, PN 400/E20,

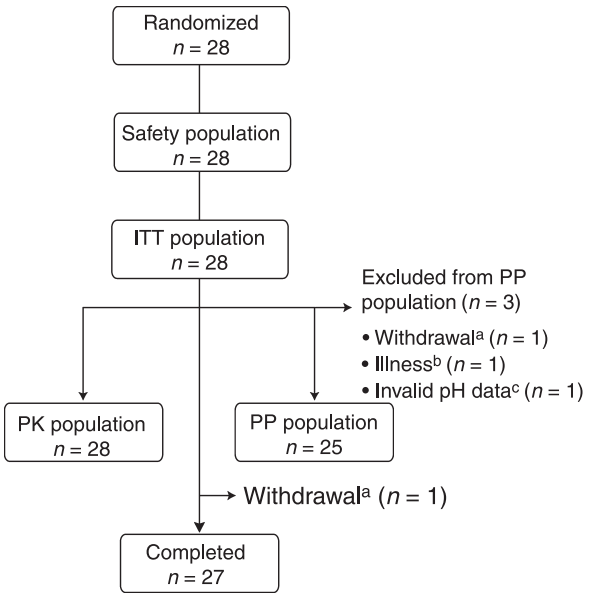

Figure 1 | Subject disposition. [a]Premature withdrawal for personal reasons; [b]On day 9 of period 4 (PN 400/E20) prior to completion of pH monitoring; [c]On day 9 of period 3 (naproxen + EC E20). ITT, intent-to-treat; PK, pharmacokinetic; PP, per protocol.

Table 2 | Baseline demographics (ITT population)

	Total participants (*n* = 28)
Age (years)	
Mean (s.d.)	24.9 (3.9)
Median	24
Range	18–34
Gender, *n* (%)	
Male	19 (68)
Female	9 (32)
Race, *n* (%)	
White	28 (100)
Height (inches)	
Mean (s.d.)	70.1 (4.1)
Median	70.0
Range	63–79
Weight (lb)	
Mean (s.d.)	177.9 (34.6)
Median	178.0
Range	112–250

ITT, intent-to-treat; s.d., standard deviation.

PN 400/E10 and naproxen + EC E20 respectively) (Table 3), although a similar pattern was observed with PN 400/E30 treatment, resulting in a greater percentage of time with intragastric pH >4.0 over 24 h compared with naproxen + EC E20 treatment (95% CI: 0.0–12.7).

As expected, compared with values reported for the percentage of time with intragastric pH >4.0 over 24 h, these percentages were higher for pH >3.0 and lower for pH >5.0 for all treatment groups on days 1 and 9 (data not shown). However, a similar treatment pattern was observed, with greater percentages reported for the PN 400/E30 and PN 400/E20 treatment groups compared with the naproxen + EC E20 treatment group.

On day 1, mean intragastric pH was low, ranging between pH 1.0 and 2.0, following an overnight fast and prior to any treatment (Figure 2b). By day 9, the range following overnight fast had increased to pH 2.0–3.0 for all treatments (Figure 2a).

Three pH surges were observed over 24 h on days 1 and 9, occurring approximately 1 h after food intake for all treatments at 1, 6 and 11 h (Figure 2). On day 9, esomeprazole in all treatments was observed to have a dose-related effect on gastric pH beyond the influence of

Table 3 | Percentage of time with gastric pH >4.0 over 24 h on days 9 and 1 (PP population)

	Day 9				Day 1			
Time pH >4.0 (%)	PN 400/E30, *n* = 25	PN 400/E20, *n* = 25	PN 400/E10, *n* = 25	Naproxen + EC E20, *n* = 25	PN 400/E30, *n* = 25	PN 400/E20, *n* = 25	PN 400/E10, *n* = 24	Naproxen + EC E20, *n* = 25
Mean (s.d.)	76.5 (12.3)	71.4 (13.0)	40.9 (22.5)	56.9 (10.1)	27.8 (22.6)	20.5 (16.6)	12.8 (11.1)	21.3 (13.6)
Median	78.8	70.4	35.8	55.1	20.0	15.3	9.1	16.8
% coefficient of variation	16	18	55	18	81	81	87	64
Range	49.8–95.3	51.8–97.6	10.3–85.3	40.6–75.5	1.8–89.6	4.4–74.4	3.0–53.8	3.2–58.2
LS mean (S.E.)	76.8 (3.0)	71.5 (3.0)	41.1 (3.0)	57.2 (3.0)	27.9 (3.3)	20.6 (3.3)	12.7 (3.4)	21.5 (3.3)
LS mean difference vs. naproxen + EC E20 (S.E.)	19.5 (3.3)	14.2 (3.3)	−16.1 (3.3)	-	6.4 (3.2)	−0.92 (3.2)	−8.9 (3.2)	-
95% CI	13.0–26.0	7.8–20.7	−(22.3–9.7)	-	0.0–12.8	−(7.3–5.4)	−(15.3–2.4)	-

PP, per protocol; EC, enteric coated; s.d., standard deviation; LS, least-squares; S.E., standard error; CI, confidence interval.

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