PN 400
(NAPROXEN AND ESOMEPRAZOLE)
PN400-104

A RANDOMIZED, OPEN-LABEL, 4-WAY CROSS-OVER STUDY TO EVALUATE THE EFFECT OF TWICE DAILY ORAL ADMINISTRATION OF THREE PN 400 DOSE COMBINATIONS (NAPROXEN 500 MG COMBINED WITH ESOMEPRAZOLE 10, 20, OR 30 MG) VS. TWICE DAILY ORAL ADMINISTRATION OF 500 MG NAPROXEN AND ONCE DAILY ORAL ADMINISTRATION OF EC ESOMEPRAZOLE (20 MG) ON THE DAY 9 24-HOUR INTRAGASTRIC PH IN HEALTHY VOLUNTEERS

FINAL CLINICAL STUDY REPORT

Product:	*PN 400 (naproxen and esomeprazole)*
IND Number:	*76,301*
Developmental phase of study:	*Phase 1*
Study Sponsor:	*POZEN Inc.* *1414 Raleigh Rd. Suite 400* *Chapel Hill, NC 27517* *(919) 913-1030*
Study Initiation Date:	*03 April 2007*
Study Completion Date:	*25 June 2007*
Release date of report:	*26 September 2008*
Sponsor's Medical Officer:	*Joseph DeVaugh-Geiss, MD*
Sponsor Signatory:	*Everardus Orlemans, PhD*

GCP STATEMENT:

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

CONFIDENTIALITY:

SIGNATURE PAGE

Study Title: A Randomized, Open-Label, 4-Way Cross-Over Study to Evaluate the Effect of Twice Daily Oral Administration of Three PN 400 Dose Combinations (Naproxen 500 mg combined with Esomeprazole 10, 20, or 30 mg) vs. Twice Daily Oral Administration of 500 mg Naproxen and Once Daily Oral Administration of EC Esomeprazole (20 mg) on the Day 9 24-Hour Intragastric pH in Healthy Volunteers

Protocol Number: PN400-104

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2. SYNOPSIS

Name of Sponsor/Company: POZEN Inc. Name of Finished Product: PN 400 Name of Active Ingredients: naproxen and esomeprazole	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study: A Randomized, Open-Label, 4-Way Cross-Over Study to Evaluate the Effect of Twice Daily Oral Administration of Three PN 400 Dose Combinations (Naproxen 500 mg combined with Esomeprazole 10, 20, or 30 mg) vs. Twice Daily Oral Administration of 500 mg Naproxen and Once Daily Oral Administration of EC Esomeprazole (20 mg) on the Day 9 24-Hour Intragastric pH in Healthy Volunteers

Investigator: Philip Miner, Jr., MD

Study center: Oklahoma Foundation for Digestive Disease Research, 1000 N. Lincoln Blvd. Suite 210, Oklahoma City, OK 73104

Publications: none

Study period:	**Phase of development:**
Date first subject enrolled: April 3, 2007 Date last subject completed: June 25, 2007	Phase 1

Objectives:

Primary: To compare the pharmacodynamic (PD) measurements of intragastric pH (percent time of pH > 4.0) on Day 9 of three PN 400 dose combinations following twice daily (bid) administration versus a combination of enteric-coated (EC) naproxen taken bid and EC esomeprazole (20 mg) taken once daily.

Secondary:

- To compare the PD measurement of intragastric pH (percent time of pH > 4.0) on Day 1 of three PN 400 dose combinations following bid administration versus a combination of EC naproxen taken bid and EC esomeprazole taken once daily
- To assess the pharmacokinetics of esomeprazole and naproxen on Day 1 and Day 9 in each of the treatment groups
- To evaluate the safety of each of the treatment groups

A non-EC naproxen formulation was inadvertently used instead of the protocol-planned EC naproxen.

Methodology: This was a randomized, open-label, 4-way crossover, single-center study in 28 healthy adults designed to compare the effect of three formulations of PN 400 (delayed-release naproxen 500 mg combined with immediate-release esomeprazole 10, 20 or 30 mg) with co-administration of enteric-coated (EC) naproxen and esomeprazole on intragastric pH. All other study medications were verified to be correct. The study consisted of four 9-day treatment periods, with a washout period of at least 12 days between treatment periods. Clinical laboratory tests, physical examination, and measurement of vital signs were performed at Screening and the Final Visit. A 12-lead electrocardiogram (ECG) and ^{13}C-urea breath test to

screen for possible *Helicobacter pylori* infection were performed at Screening. A urine drug screen for all subjects and a urine pregnancy test for women of childbearing potential were performed at Screening and on Days 0 and 8 of each treatment period. On Days 1 and 9 of each treatment period, 24-hour blood sampling was performed for pharmacokinetic (PK) assessments.
At any time during Screening, subjects had their lower esophageal sphincter (LES) located to determine accurate placement of the pH probe. Subjects were randomized on Day 1 of the first treatment period into 1 of 4 dosing sequences to receive a 9-day course of each one of the following daily treatment regimens in a crossover fashion: • Treatment A: 1 tablet PN 400 (naproxen 500 mg/esomeprazole 30 mg) bid (PN 400/E30) • Treatment B: 1 tablet PN 400 (naproxen 500 mg/esomeprazole 20 mg) bid (PN 400/E20) • Treatment C: 1 tablet PN 400 (naproxen 500 mg/esomeprazole 10 mg) bid (PN 400/E10) • Treatment D: 1 tablet of naproxen 500 mg and 1 tablet EC esomeprazole 20 mg in the AM and 1 tablet of naproxen 500 mg in the PM (EC E20 + naproxen) All treatments were administered 60 minutes prior to meals by study personnel. Prior to administration of the Day 1 AM dose of study drug, the pH probe was placed to monitor intragastric pH for a period of 24 hours. In addition, a pre-AM dose blood sample and serial post-AM blood samples were obtained over the next 24 hours. The pH probe was removed in the morning on Day 2 prior to AM dosing. After AM dosing on Day 2, subjects were discharged from the Phase 1 unit and instructed to return for the next dosing in the PM of Day 2 and on Days 3-8 to receive the AM and PM doses. Subjects were again confined to the Phase 1 unit in the PM of Day 8 in preparation for the 24-hour PK and pH assessments on Day 9. The pH probe was removed in the AM on Day 10. Final PK samples were collected in the AM of Day 10. In each subsequent treatment period, the same procedures were performed as during the first period, and final study procedures were performed on Day 10 of the last treatment period or whenever a subject discontinued from the study.
Number of subjects (planned and analyzed): 28 subjects were planned, randomized and treated, and data for 25 subjects were analyzed as the Per-Protocol (PP) population; the Intent-to-Treat (ITT), Safety and PK populations included all 28 subjects.
Diagnosis and main criteria for inclusion: Subjects were healthy males or non-lactating, non-pregnant females 18 to 55 years of age with a body mass index of 19-32 kg/m^2, were *Helicobacter pylori* (*H. pylori*) negative, and were generally in good health with no history of peptic ulcer disease or other acid-related gastrointestinal (GI) symptoms.
Test product, dose and mode of administration, batch number: PN 400 (combination tablets of delayed-release naproxen 500 mg/immediate-release esomeprazole 10, 20 or 30 mg), Batch numbers [redacted], [redacted] and [redacted] respectively, given by mouth bid for 9 days
Duration of treatment: 4 treatment periods of 9 days each
Reference therapy, dose and mode of administration, batch number: Naproxen 500 mg tablets (Lot # HA08607, Glenmark Pharmaceuticals, Ltd., expiration date 12/2010) given by mouth bid for 9 days along with EC esomeprazole 20 mg tablets (Lot # U4149, Astra Zeneca, expiration date 09/2009) given by mouth once daily for 9 days. A non-EC naproxen formulation was inadvertently used instead of the protocol-planned EC naproxen.

Criteria for evaluation:

Pharmacodynamics: Intragastric pH monitoring

Pharmacokinetics: Full plasma profiles of naproxen and esomeprazole over the 24-hour post-AM dose period on Day 1 and Day 9.

Safety: Adverse event assessment, clinical laboratory tests (hematology, chemistry, urinalysis, urine drug screen, and pregnancy test for women of childbearing potential), vital signs, physical examination, 12-lead ECG.

Endpoints and statistical methods:

Sample size: From a previous AstraZeneca study, the within-subject standard deviation (SD) of percent time of pH > 4.0 was 10%. The current study planned to enroll 28 subjects with the aim to have 24 evaluable subjects for analysis. A total of 24 subjects provides 80% power to reject the null hypothesis that the difference between each of the PN 400 treatments and the active control in percent time of pH > 4.0 over 24 hours is ≤ -8% using a pairwise t-test with a one-sided significance level of 0.05.

Pharmacodynamics:

Primary Endpoint: Percent time intragastric pH > 4.0 on Day 9

Secondary Endpoint: Percent time intragastric pH > 4.0 on Day 1

Endpoints were summarized by treatment and analyzed by Analysis of Variance (ANOVA). The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. The least square (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. The PP population was the primary analysis population.

Pharmacokinetics:

PK parameters for esomeprazole were determined following the three different PN 400 treatments and PK parameters for naproxen were determined following each of the 4 treatments included peak plasma concentration (C_{max}) on Days 1 and 9, time to peak plasma concentration (t_{max}) on Days 1 and 9, area under the plasma concentration vs. time curve from time zero to the last time point with measurable drug concentration (AUC_{0-t}) on Days 1 and 9, and the terminal half-life ($t½$), if possible, following both the AM and PM doses on Days 1 and 9. In addition, the AUC from time zero (time of dosing) to 10 hours post-AM dose ($AUC_{0-10,am}$) and AUC from time zero (time of dosing) to 14 hours post-PM dose ($AUC_{0-14,pm}$) and a total daily AUC (AUC_{0-24}) were determined on Days 1 and 9. PK parameters for esomeprazole following EC E20 + naproxen included C_{max}, t_{max}, AUC_{0-t}, $t½$, and AUC_{0-24} following the AM dose on both Days 1 and 9. Statistical analysis was performed using Analysis of Variance (ANOVA) to determine the point estimate and 90% CI of the Day 9 to Day 1 ratios for the following parameters for both naproxen and esomeprazole $C_{max,am}$, $C_{max, pm}$, $AUC_{0-10, am}$, $AUC_{0-14, pm}$, and AUC_{0-24}.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) for system organ class (SOC) and preferred term. Adverse events were summarized by treatments, SOC and preferred term. Tabulations and listings of values for vital signs, clinical laboratory tests, and abnormal physical examination findings were prepared. Laboratory values for each subject were listed with abnormal values flagged.

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