CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22511Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of New Drugs Quality Assessment
BIOPHARMACEUTICS REVIEW - ADDENDUM

NDA#:	22-511/N-000
Submission Date:	03/04/10 (Amendment 0009) and 04/23/10 (Amendment 0014)
Brand Name:	Vimovo
Generic Name:	Naproxen/Esomeprazole
Formulation:	Naproxen Delayed release (DR)/Esomeprazole (Eso) magnesium immediate release (IR) fixed dose combination (FDC) tablets
Strength:	500/20 mg and 375/20 mg
Sponsor:	Pozen
Type of submission:	Amendment to NDA
Reviewer:	Tien-Mien Chen, Ph.D.

SUBMISSION

Reference is made to NDA 22-511 for VIMOVO (naproxen/esomeprazole) 375 mg/20 mg and 500 mg/20 mg Tablets submitted on June 30, 2009, and to the Biopharmaceutics review comments sent to the applicant on April 19, 2010. Reference is also made to the teleconferences held between the applicant and FDA on

1). Feb. 24, 2010, in which the phase 4 commitment on dissolution methodology for VIMOVO Tablets was discussed, and

2). April 21, 2010, in which the dissolution specifications for VIMOVO Tablets on an interim basis (within one year post approval) were discussed.

ADDENDUM

The main objective of this Addendum to the previous Biopharmaceutics Review (in DARRTS dated March 8, 2010) for NDA 22-511 is to document the dissolution specifications that were agreed on with the applicant in the teleconference held on April 21, 2010. Based on this agreement the following dissolution method and specifications will be used on an interim basis for one year for VIMOVO Tablets, 375 mg/20 mg and 500 mg/20 mg.

Acid Stage:

Naproxen only

Acid stage testing determines the acid resistance of the enteric-coated naproxen core tablet.

Dissolution Method

USP Apparatus 2 (with sinkers) at 75 rpm

Medium: 475 mL of 0.1 M HCl at 37°C

Dissolution Specification:

NMT (b) (4) at 2 hours (Meets USP Requirements)

<u>Buffer Stage:</u>
Esomeprazole and Naproxen
(*Using a second set of tablets***)**

Dissolution Method
USP Apparatus 2 (with sinkers) at 75 rpm
Medium: 900 mL of 0.05 M phosphate buffer pH 7.4 at 37°C

Dissolution Specifications:
Q= (b) (4) at 60 minutes for Naproxen
Q= (b) (4) at 60 minutes for Esomeprazole

Regarding the final dissolution methodology for VIMOVO Tablets, the applicant previous Phase 4 commitment (submitted on March 4, 2010, Sequence #0009) to develop a method to test the naproxen component continuously (i.e. acid then buffer testing on the same set of tablets), remains unaffected. Additionally, the applicant agreed to generate dissolution profile data on multiple batches for both components and submit after one year a proposal for the final dissolution specifications based on the generated data.

_____ _____04/24/10, 04/26/10___
Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____04/24/10, 04/26/10___
Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
04/28/2010

PATRICK J MARROUM
04/28/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22511	Submission Date(s): 06/30/2009
Brand Name	Vimovo®
Generic Name	Naproxen / Esomeprazole Magnesium
Reviewers	PeiFan Bai, Ph.D., Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	POZEN Inc
Submission Type; Code	NDA 505 (b) (2), Original
Formulation; Strength(s)	Tablets; EC naproxen 375 mg/IR esomeprazole 20mg; EC naproxen 500 mg/IR esomeprazole 20 mg
Indication	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.
Dosing Regiment	One tablet, twice daily

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1 Executive Summary

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor.

1.2 Phase IV Commitments

As a part of PREA requirement, the sponsor should conduct PK studies in pediatric population, 2-17 years of age.

1.3 Regulatory Background

Vimovo® has an immediate release (IR) esomeprazole magnesium layer and an enteric coated (EC) naproxen core. Being a 505 b(2) application, this NDA references two FDA-approved products as listed below.

Name of Drug	NDA #	Sponsor	Strength	Approved Year
EC Naprosyn	020067	Roche	375 mg and 500 mg	1994
Nexium Capsules	021153	AstraZeneca	20 mg and 40 mg	2001

Currently, EC-NAPROSYN® (naproxen delayed-release tablets) is available as enteric coated tablets containing 375 mg of naproxen or 500 mg of naproxen for oral administration. Nexium® (esomeprazole magnesium) is available as delayed-release capsules and delayed-released oral suspension. For the indication of risk reduction of NSAID-associated gastric ulcer, both 20 mg and 40 mg are approved for once daily for up to 6 months The Nexium® formulation used for comparison in this NDA submission is 20 mg delayed-release capsules.

NOTE: In this review, Vimovo and PN 400 will be used inter-exchangeably.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Dose selection:

EC-Naprosyn is approved for the indications of Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis at both 500 mg and 375 mg doses for twice daily administration. Esomeprazole is approved for risk reduction of NSAID-associated gastric ulcer 20 mg or 40 mg once daily for up to 6 months. The sponsor's rationales for clinically study the 20 mg bid dose for esomeprazole are 1) after 2 weeks of bid dosing, esomeprazole 20 mg resulted in a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza Score of 0) as compared to 10 mg or 30 mg of esomeprazole, and 2) After 9 days of bid dosing, esomeprazole 20 mg resulted in a greater percent time with intragastric pH > 4.0 than esomeprazole 10 mg (71.4% vs 40.6%).

Bioequivalence with respect to naproxen and relative bioavailability of esomeprazole:

At 375 mg dose of naproxen, PN 400 was bioequivalent to EC-NAPROSYN®. At 500 mg dose of naproxen, the first bioequivalence study with less frequent sampling failed to demonstrate bioequivalence (BE) for C_{max}. With more frequent sampling in a second bioequivalence study,

PN 400 was bioequivalent to EC NAPROSYN ®. We concluded that Vimovo is bioequivalent to EC-NAPROSYN®. At 20 mg, average esomeprazole AUC following Vimovo was approximately 50% of that following Nexium, indicating that immediate release of esomeprazole without protection against gastric acidic degradation resulted in significantly lower esomeprazole exposure.

Drug-drug intreractions, pharmacokinetics, and pharmacodynamic characteristics:
Co-administration of naproxen and esomeprazole in PN 400 did not alter the PK profile of either drug regardless of esomeprazole formulation (IR or EC), suggesting the absence of pharmacokinetic drug-drug interaction between naproxen and esomeprazole.

The afternoon dose had lower esomeprazole AUC and Cmax than the morning dose. AUC and Cmax following multiple doses were higher than following single dose. Esomeprazole component of PN 400 has very high inter- and intra-individual variability regardless of single dose or multiple dose administration.

Mean % time pH>4 following Vimovo increased with esomeprazole dose with 41%, 71%, and 77%, for 10 mg, 20mg, and 30 mg, respectively.

Food Effect
High-fat meal significantly reduced esomeprazole bioavailability by 50% and delayed naproxen absorption by 10 hr from Vimovo. When Vimovo was administered 30 min or 60 min prior to food intake, food had less effect on esomaprozole and naproxen absorption. This observed food effect was taken into consideration in Phase III clinical trials as patients were instructed to take Vimovo 30-60 min before breakfast or dinner.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of Vimovo® (PN 400 tablet) formulation?

Vimovo® (PN 400 tablet) is an oral fixed dose combination product (tablet) containing 375 mg or 500 mg naproxen in the enteric coated core (delayed release) surrounded by 20 mg esomeprazole (22.3 mg magnesium trihydate) in the immediate-release film coat.

2.1.2 What is the proposed indication of Vimovo® ?

PN 400 tablet is indicated 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.

2.1.3 What are the proposed mechanisms of actions of Vimovo?

Vimovo is a combination drug product of naproxen and esomeprazole.

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclo-oxygenase (COX) enzyme activity which reduces prostaglandin synthesis resulting in anti-inflammatory, analgesic and anti-pyretic activity.

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion via specific inhibition of the H^+, K^+-ATPase enzyme (proton pump) located in the secretory membrane of the gastric parietal cell. Esomeprazole does not exhibit anticholinergic or H2 histamine antagonistic properties. In the acidic compartment of the parietal cell, esomeprazole is protonated and converted into a pharmacologically active inhibitor that react with luminally accessible cysteines of H^+, K^+-ATPase to form a disulfide bond, thus irreversibly inhibiting H^+, K^+-ATPase activity. Since PPIs block the final common pathway of acid production in the stomach, they inhibit both basal and stimulated gastric acid secretion. According to the sponsor, esomeprazole was selected as the PPI of choice because of its superior acid inhibiting properties compared to other marketed PPIs and its proven efficacy in risk reduction of NSAID-associated gastric ulcers.

2.1.4 What are the proposed dosage and route of administration?

The combination product Vimovo® is available as EC naproxen 375 mg/ IR esomeprazole 20 mg tablet and EC naproxen 500 mg/ IR esomeprazole 20 mg tablet. The proposed route of administration for all the indications sought approval is oral; the proposed daily dosing regimen is one tablet twice daily. Use the lowest effective dose. Not recommended in moderate/severe renal insufficiency or in severe hepatic insufficiency. Consider dose reduction in mild/moderate hepatic insufficiency.

2.1.5 What is the sponsor's dose selection rationale?

EC-Naprosyn is approved for the indications of Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis at both 500 mg and 375 mg doses for twice daily administration. Esomeprazole is approved for risk reduction of NSAID-associated gastric ulcer 20 mg or 40 mg Once daily for up to 6 months. The sponsor's rationales for choosing the 20 mg bid dose are 1) After 2 weeks of bid dosing, PN 400 containing an esomeprazole dose of 20 mg resulted in a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza Score of 0) compared to PN 400 formulations containing 10 mg or 30 mg of esomeprazole or naproxen alone (range 5.3-15%); 2) After 9 days of bid dosing, PN 400 containing esomeprazole 20 mg treatment resulted in a greater percent time with intragastric pH > 4.0 (71.4% time with gastric pH > 4.0) than PN 400 containing esomeprazole 10 mg (40.6%).

2.1.6 What is the regulatory background?

This NDA is a 505 b(2) application with two reference-listed products shown below.

Reference listed drug(s)

Name of Drug	NDA #	Sponsor	Strength	Approved Year
EC Naprosyn	020067	Roche	375 mg and 500 mg	1994
Nexium Capsules	021153	AstraZeneca	20 mg	2001

Currently, EC-NAPROSYN® (naproxen delayed-release tablets) is available as enteric coated tablets containing 375 mg of naproxen or 500 mg of naproxen for oral administration. Nexium® (esomeprazole magnesium) is available as delayed-release capsules and delayed-released oral suspension. The Nexium® formulation used for comparison in this NDA submission is 20 mg delayed-release capsules.

The clinical efficacy of Vimovo in treating osteoarthritis, rheumatoid arthritis, and ankylosing spondyliti was established in part through the demonstration of bioequivalence of naproxen component to enteric-coated naproxen, Naprosyn®. The sponsor conducted 3 studies (PN400-102, PN400-114, and PN400-105) to demonstrate bioequivalence on the naproxen component in Vimovo tablets with EC-Naprosyn. Per our request during the End-of-Phase II meeting on 17 July 2007, the sponsor conducted a relative bioavailability study for the esomeprazole component.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of clinical pharmacology and clinical studies used to support the dosing and efficacy claim?

The naproxen dose strengths in PN400, 375 mg and 500 mg, correspond to those approved for Naprosyn®. Bioequivalence of naproxen in Vimovo (PN 400) as compared to Naprosyn® was evaluated in 3 separate phase I studies.

Bioequivalence of naproxen component of PN 400 at 375 mg was evaluated in an open-label, randomized, single oral dose, two-way crossover study with 30 healthy volunteers (PN 400-105), in which PK and relative BA of naproxen was compared from a single oral dose of PN 400 (naproxen 375 mg/ esomeprazole 20 mg) and a single oral dose of EC-ECNAPROSYN® 375 mg. The result of this study supported the bioequivalence of PN 400 with EC-NAPROSYN in terms of naproxen component at 375 mg dose.

The bioequivalence of naproxen at 500 mg was evaluated in 2 studies.
Study PN400-102 was the first bioequivalence study at 500 mg naproxen dose, which was a randomized, open-label, three-way crossover study in 36 subjects at a single center in the United States. The washout period was at least 8 days. The primary objective was to assess and compare the pharmacokinetics and relative bioavailability of a single oral dose of naproxen 500 mg administered in three formulations (PN 400, the naproxen component of PN 400, and EC-NAPROSYN®) in healthy volunteers. The study design is considered acceptable.

The second bioequivalence study at 500 mg naproxen dose was a randomized, open-label, single oral dose, 4-way crossover study where 37 healthy subjects completed the study with 3 formulations (PN 400 (delayed-release naproxen 500 mg /immediate-release esomeprazole 20 mg), EC naproxen 500 mg tablet (EC Naprosyn®) plus EC esomeprazole 20 mg capsule (Nexium®), and the EC naproxen 500 mg tablet (EC Naprosyn®) alone).

The effect of food and timing of food intake on bioavailability of naproxen and esomeprazole from PN 400 was evaluated in phase I, open-label, randomized, single-dose, 4-way crossover study in 21 healthy volunteers utilizing the standard high-fat breakfast.

Study PN400-101 was a Phase 1, randomized, investigator-blinded, open-label, parallel-group, active controlled study conducted in a single center in 80 healthy volunteers. EC Naprosyn® 500 mg tablets were the comparator. The primary objective was to evaluate the risk of naproxen associated gastroduodenal injury of three PN 400 dose combinations, as determined by combined gastric and duodenal Grade 3 or 4 lesions
One secondary objective was to assess the pharmacokinetics of esomeprazole on Day 1 and Day 14 in each of the PN 400 treatment groups, and the pharmacokinetics of naproxen on Day 1 and Day 14 in all treatment groups. The study design is considered acceptable.

Study PN400-104 was a randomized, open-label, 4-way crossover, single-center study in 28 healthy adults comparing the effect on intragastric pH of three esomeprazole dose levels formulated in PN 400 with a treatment of non-EC naproxen plus EC esomeprazole. Hereafter, the non-EC naproxen of the control treatment is referred to as naproxen. The objective was to compare the pharmacodynamic (PD) measurements of intragastric pH (percent time intragastric pH > 4.0) on Day 9 of three PN 400 dose levels following twice-daily (bid) administration versus a combination of EC naproxen taken bid and EC esomeprazole taken once daily. The study consisted of four 9-day treatment periods. The first, second and third treatment periods were followed by a washout period of 12 days. Considering a plasma half-life of 1.5 hrs for esomeprazole, a plasma half-life of 12-17 hrs for naproxen, and a regular and constant turnover of H+/K+ ATPases, which in humans have a half-life of 2–3 days, the washout period of 12 days is considered acceptable.

The efficacy and safety of PN 400 in reduction of gastric ulcer occurrence was evaluated in 2 pivotal 6-month, Phase III, double blind, parallel group, randomized, active controlled, multi-center study where subjects took either PN400 (500 mg naproxen/20 mg esomeprazole) tablet BID or EC naproxen 500 mg tablet BID on a daily basis.

Long term safety of PN 400 was evaluated in a 12-month, phase III, open –label, multi-center study.

2.2.2 What was the clinical endpoint in the Phase 3 trials?

The pivotal efficacy and safety studies had following endpoints:

The primary endpoint:

- The cumulative proportion of subjects developing endoscopically visualized gastric ulcers (GU) through 6 months of treatment with PN 400 tablets relative to the EC naproxen control. Endoscopies were conducted at baseline and at 1, 3 and 6 months of treatment.

The key secondary endpoints:

- Pre-specified NSAID-associated UGI AEs and/or duodenal ulcers,
- Discontinuation from study due to NSAID-associated UGI AEs or to duodenal ulcers
- The overall incidence of duodenal ulcers diagnosed endoscopically throughout the 6 months of study treatment.

2.2.3 What are the PK characteristics of PN 400 and its individual components following single oral dose?

All of the following pharmacokinetic parameters were determined using non-compartmental analysis from the plasma concentration vs. time profile.

Naproxen PK at 375 mg in healthy subjects:

In PN 400-105, 30 healthy volunteers received single dose of either PN 400 (375 mg naproxen/ 20 mg esomeprazole) or EC- NAPROSYN® 375 mg in a crossover study design following an overnight fasting of at least 10 hr. No food was allowed for at least 4 hours post-dose.

Summary of Naproxen Pharmacokinetic Parameters at 375 mg by Treatment:

Treatment	Statistics	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-inf} (hr*µg/mL)	$t_{½}$ (hr)
A PN 400 375 mg (N = 30)	Mean	57.9	4.73	977	1060	19.8
	% CV	17	36	15	17	14
B EC-NAPROSYN® 375 mg (N = 30)	Mean	56.9	5.02	1003	1084	19.3
	% CV	21	84	15	17	15

Naproxen PK at 500 mg in healthy subjects:

In study PN 400-114, the sponsor evaluated the naproxen pharmacokinetic profile following a single oral dose administration of either PN 400 (500 mg naproxen/ 20 mg esomeprazole) or EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM) or EC-NAPROSYN 500 mg tablet alone to healthy volunteers following overnight fasting of at least 10 hrs. No food was allowed for at least 4 additional hours after the dose administration.

Summary of Naproxen Pharmacokinetic Parameters at 500 mg by Treatment:

Treatment	Statistics	C_{max} (µg/mL)	T_{max} (hr)	T_{lag} (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-inf} (hr*µg/mL)	$t_{½}$ (hr)
A PN 400 (N = 38)	Mean	66.9	6.15	1.98	1226	1326	18.9
	%CV	22	58	53	15	17	14
B EC Naproxen +EC Eso (N = 39)	Mean	74.3	4.95	1.22	1263	1374	19.6
	%CV	22	96	88	15	17	14
C EC Naproxen (N = 39)	Mean	75.3	4.99	1.69	1266	1375	19.4
	%CV	20	85	69	15	16	11

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM)
Treatment C: EC-NAPROSYN 500 mg tablet

Naproxen PK parameters at 500 mg were also evaluated in study PN 400-102 and PN 400-103. In study PN 400-102, AUC and half life of naproxen from PN 400 and commercially available EC-NAPROSYN 500 mg table were comparable to the result from study PN 400-114; However, due to difference in sampling frequency, C_{max} and T_{max} from study PN 400-102 were slightly different from results of study PN 400-114. PK parameters of naproxen from PN 400 from study PN 400-103 (food effect study) were comparable to the study result of PN 400-114.

Summary of Naproxen PK Parameters at 500 mg by different studies:

Study Treatment	Statistics	C_{max} (µg/mL)	T_{max} (hr)	T_{lag} (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-inf} (hr*µg/mL)	$t_{½}$ (hr)
PN 400-114 PN 400	Mean	66.9	6.15	1.98	1226	1326	18.9
	%CV	22	58	53	15	17	14
PN 400-114 EC Naproxen	Mean	75.3	4.99	1.69	1266	1375	19.4
	%CV	20	85	69	15	16	11
PN 400-102 PN 400	Mean	57.6	7.07		1178	1290	19.3
	%CV	25	69		19	22	18
PN 400-102 EC Naproxen	Mean	66.6	5.78		1285	1415	20.2
	%CV	20	79		19	23	16
PN 400-103 (Food effect Study)	Mean	62.4	6.1	2.00	1135	1220	18.8
	%CV	19	55	49	10	12	10

Esomeprazole PK parameters in healthy subjects:

Esomeprazole (20 mg) pharmacokinetics parameters were evaluated in several different studies.
In study PN 400-114, the sponsor evaluated the esomeprazole pharmacokinetic profile following a single oral dose administration of either PN 400 (500 mg naproxen/ 20 mg esomeprazole) or EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM) or EC-Esomeprazole capsule (Nexium®) alone to healthy volunteers following overnight fasting of at least 10 hrs and continued fasting for 4 additional hours after dosing.

Summary of Esomeprazole (20 mg) Pharmacokinetic Parameters by treatment:

Treatment	Statistics	C_{max} (ng/mL)	T_{max} (hr)	T_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
A PN 400 (N = 38)	Mean	425	0.51	0.03	465	467	0.971
	%CV	81	49	234	91	91	45
B EC Naproxen +EC Eso (N = 39)	Mean	432	2.50	0.91	801	803	0.945
	%CV	48	54	134	79	79	49

D EC Esomeprazole (N = 39)	Mean	455	2.43	0.87	806	815	0.936
	%CV	40	34	47	78	81	44

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM)
Treatment D: EC-Esomeprazole 20 mg capsule (Nexium®)

The results of esomeprazole PK parameters from other studies (PN 400-103, 105, 111) following the administration of PN 400 were comparable with the results from study PN 400-114 that they all had a very high PK variability.

Summary of Esomeprazole (20 mg) Pharmacokinetic Parameters by different studies:

Study Treatment	Statistics	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
PN 400-114 PN 400	Mean	425	0.51	465	467	0.971
	%CV	81	49	91	91	45
PN 400-103 PN 400	Mean	464	0.57	576	579	1.06
	%CV	80	41	80	79	33
PN 400-105 PN 400	Mean	424	0.52	566	569	1.04
	%CV	86	35	128	128	39
PN 400-111 PN 400	Mean	383		383	385	0.99
	%CV	87		97	97	27

2.2.4 What are the pharmacokinetics of esomeprazole and naproxen following one-day and multiple-day administrations?

The primary objective of study PN400-101 was to evaluate the risk of naproxen associated gastroduodenal injury of three PN 400 dose levels. The secondary objective was to assess the pharmacokinetics of esomeprazole on Day 1 and Day 14 in each of the PN 400 treatment groups, and the pharmacokinetics of naproxen on Day 1 and Day 14 in all treatment groups. No food was allowed after midnight prior to the am dose on days 1 to 14. On Days 1 to 14 no food was allowed 2 hours prior to the PM dose. Each dose of study medication was administered 60 minutes prior to breakfast (for the AM dose) and 60 minutes prior to dinner (for the PM dose). From the clinical pharmacology perspective, our review will focus only on the pharmacokinetic and pharmacodynamic section. On Days 1 and 14, 24-hour blood samples were collected for PK assessments, beginning just prior to the morning dose of study medication, and continuing at the following times post-dosing: 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 (just prior to the afternoon dose), 10.17, 10.33, 10.5, 10.75, 11, 11.5, 12, 12.5, 13, 14, 16, 18, 20 and 24 hours. The 24-hr blood samples following 14 days of administration were taken in the morning of day 15.

Treatment	Treatment Name	Study Medication	Number of Subjects Planned
A	PN 400/E30	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 30 mg) bid	20
B	PN 400/E20	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 20 mg) bid	20
C	PN 400/E10	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg) bid	20
D	EC naproxen	EC naproxen 500 mg bid	20

EC Naprosyn® 500 mg tablets (naproxen delayed release tablets) were manufactured by Roche Pharmaceuticals. Treatment began on the morning of Day 1 and continued through the evening of Day 14, for a total of 28 doses. Doses on each treatment day were given approximately 10 hours apart. Study drug was swallowed each time with 240 ml of water.

Demographic characteristics of the groups

	PN 400/E30 N=20	PN 400/E20 N=20	PN 400/E10 N=20	EC Naproxen N=20
Age (years)				
Mean (SD)	52.8 (6.1)	56.1 (6.3)	52.3 (7.8)	51.9 (8.0)
Median	54.5	57.0	51.5	51.0
Range	41.0-63.0	43.0-65.0	41.0-64.0	40.0-65.0
Gender – n (%)				
Males	9 (45)	12 (60)	14 (70)	12 (60)
Females	11 (55)	8 (40)	6 (30)	8 (40)
Race – n (%)				
White	20 (100)	20 (100)	19 (95)	20 (100)
Black/African American	0	0	1 (5)	0
Asian	0	0	0	0
Other	0	0	0	0
Ethnicity – n (%)				
Hispanic or Latino	2 (10)	1 (5)	1 (5)	1 (5)
Not Hispanic or Latino	18 (90)	19 (95)	19 (95)	19 (95)

The four treatment groups have similar demographic characteristics.

Endoscopies were performed on Day -1 and Day 15. The same gastroenterologist performed all endoscopies and was blinded to the assigned treatment group for each subject. All areas of the gastric and duodenal bulb were examined and the numbers of hemorrhages, erosions, and ulcers in each location were recorded. Any ulcers were measured and the largest diameter recorded. An ulcer was defined as a mucosal break of at least 3 mm in diameter (measured by close application of open endoscopic biopsy forceps) with depth.

Grading of Stomach and Duodenal Lesions (Lanza 1988)

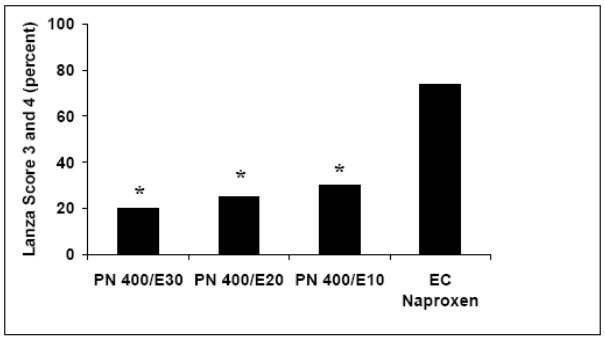
Grade	Number of Erosions, Hemorrhages, and Ulcers
0	No visible lesions
1	1 erosion or hemorrhages
2	2-10 erosions or hemorrhages
3	11-25 erosions or hemorrhages
4	>25 erosions or hemorrhages or any ulcer

Lanza Scores - Day 15/End of Study – Stomach and Duodenum Combined – Per Protocol Population.

	PN 400/E30 N=20	PN 400/E20 N=20	PN 400/E10 N=20	EC Naproxen N=19
Lanza Score, n (%)				
0 (no visible lesions)	3 (15.0)	8 (40.0)	2 (10.0)	1 (5.3)
1 (1 hemorrhage or erosion)	1 (5.0)	2 (10.0)	1 (5.0)	0
2 (2-10 hemorrhages or erosions)	12 (60.0)	5 (25.0)	11 (55.0)	4 (21.1)
3 (11-25 hemorrhages or erosions)	4 (20.0)	3 (15.0)	5 (25.0)	5 (26.3)
4 (>25 hemorrhages or erosions, or an ulcer)	0	2 (10.0)	1 (5.0)	9 (47.4)
Lanza Score = 3 or 4 at Day 15/Early Withdrawal	4 (20.0)	5 (25.0)	6 (30.0)	14 (73.7)
p-value [1] compared to EC Naproxen	0.001	0.004	0.010	--

[1] Fisher's Exact test

Percent of Subjects with a Grade 3 and 4 Lanza Score on Day 15

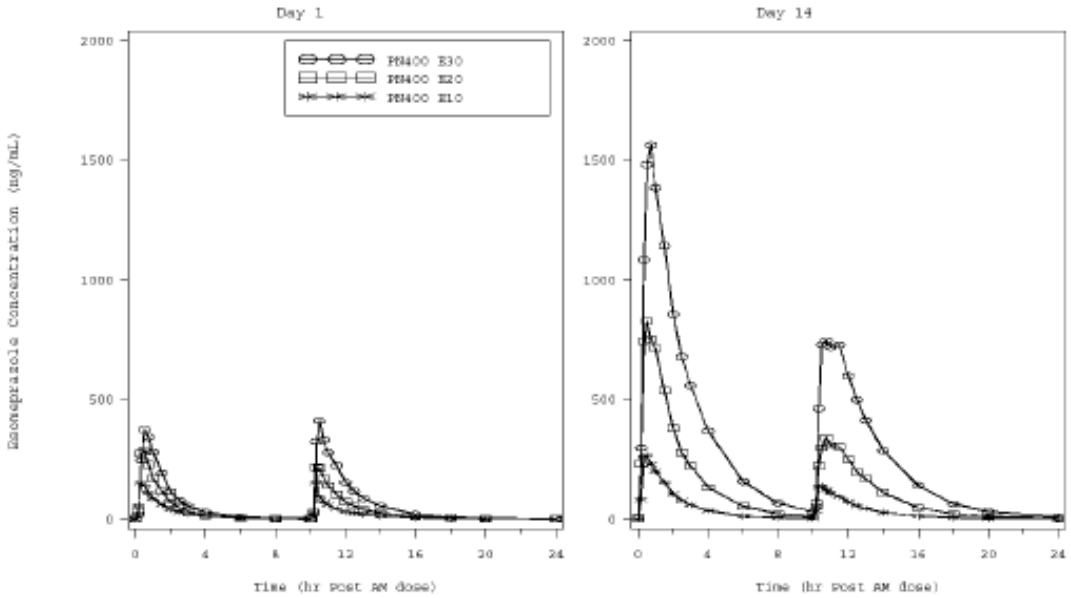


Fisher's Exact test, *p ≤ 0.01 compared to EC naproxen

Treatment differences in the distribution of Lanza scores were statistically significant in each pair-wise comparison with EC naproxen.

Esomeprazole pharmacokinetics

Mean Plasma Esomeprazole Concentration vs. Time Curves for All PN 400 Treatments on Day 1 and Day 14



Plasma esomeprazole concentrations after the PM dose were similar to those after the AM dose on Day 1, but on Day 14 esomeprazole concentrations after the PM dose were lower than those after the AM dose for each treatment. In addition, the mean/median concentrations of esomeprazole were higher on Day 14 than on Day 1, especially after the AM dose. Though esomeprazole has a short half life, its am and pm exposures on day 14 were consistently higher than the respective exposures on day 1, for each PN400 formulation.

Mean (CV%) of Esomeprazole Pharmacokinetic Parameters by Study Day and Dose Time for Treatment A (PN 400/E30)

Day, dose, N	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*ng/mL)	AUC0-24 (hr*ng/mL)	T1/2 (hrs)
Day 1, am N=20	435 (90)	0.63 (33)	594 (83)	--	0.94 (25)
Day 1, pm N=20	457 (120)	0.68 (58)	767 (119)	1361 (99)	1.06 (29)
Day 14, am N=20	1804 (26)	0.56 (40)	4161 (32)	--	1.52 (18)
Day 14, pm N=20	949 (60)	1.00 (57)	2800 (48)	6961 (36)	1.68 (22)

Mean half life (CV%) values of esomeprazole for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 0.94 hr (25%), 1.06 (29%), 1.52 (18%) , and 1.68 (22%). On day 14, the pm dose showed lower esomeprazole exposure than the am dose. AUC0-24 represents AUC from time zero (time of AM dosing) to 24 hours after the AM dose.

Mean (CV%) of Esomeprazole Pharmacokinetic Parameters by Study Day and Dose Time for Treatment B (PN 400/E20)

Day, dose, N	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*ng/mL)	AUC0-24 (hr*ng/mL)	T1/2 (hrs)

Day 1, am N=20	339 (84)	0.52 (34)	398 (88)	--	0.89 (26)
Day 1, pm N=20	246 (116)	0.60 (58)	384 (145)	781 (109)	1.06 (33)
Day 14, am N=19	1034 (35)	0.53 (44)	1874 (50)	--	1.24 (35)
Day 14, pm N=19	468 (81)	1.10 (84)	1120 (73)	2994 (57)	1.48 (36)

Mean half life (CV%) values of esomeprazole for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 0.89 hr (26%), 1.06 (33%), 1.24 (35%) , and 1.48 (36%). On day 1 and day 14 each, the pm dose showed lower esomeprazole exposure than the am dose.

Mean (CV%) of Esomeprazole Pharmacokinetic Parameters by Study Day and Dose Time for Treatment C (PN 400/E10)

Day, dose, N	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*ng/mL)	AUC0-24 (hr*ng/mL)	T1/2 (hrs)
Day 1, am N=20	164 (86)	0.43 (38)	234 (153)	--	0.87 (45)
Day 1, pm N=20	159 (139)	0.55 (82)	180 (163)	414 (154)	0.96 (47)
Day 14, am N=19	319 (59)	0.53 (57)	535 (93)	--	1.03 (39)
Day 14, pm N=19	155 (91)	0.75 (65)	346 (118)	881 (103)	1.24 (52)

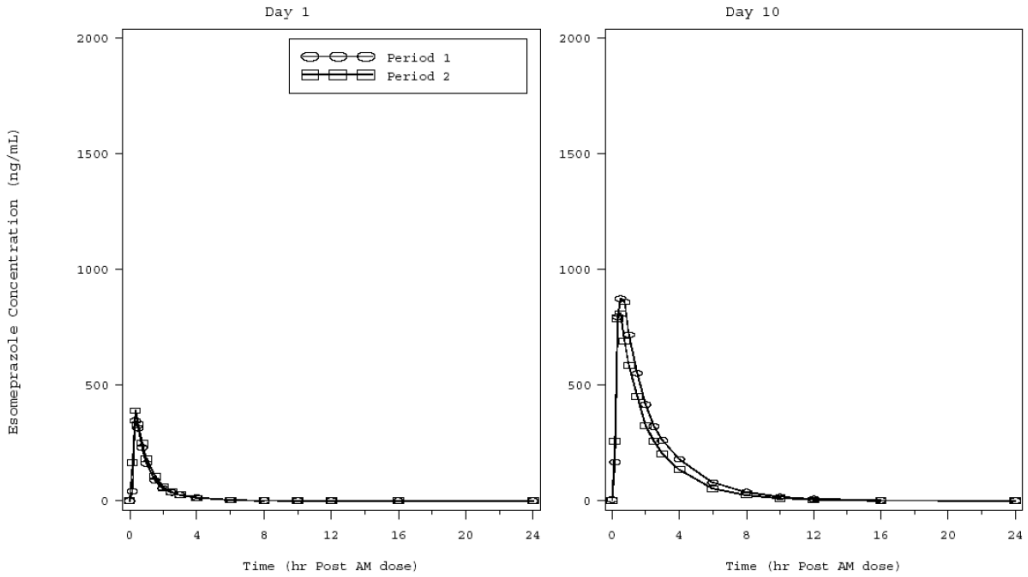
Mean half life (CV%) values of esomeprazole for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 0.87 hr (45%), 0.96 (47%), 1.03 (39%) , and 1.24 (52%).
On day 1 and day 14 each, the pm dose showed lower esomeprazole exposure than the am dose.

Reviewer's Comments: On Day 1, the AUC and Cmax of esomeprazole increased approximately proportionally with dose with high variability. The pharmacokinetics are similar to those stated in the approved Nexium labeling. The results of higher esomeprazole exposure after multiple days of administration despite of short terminal half life are consistent with what was observed for all the proton pump inhibitors approved so far.

Esomeprazole PK parameters following multiple dose of PN 400 was also evaluated in a in PN 400-111 which was a phase I, open-label, single center, 2 treatment period study following single and multiple oral dose administration of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) tablets in healthy subjects. In each treatment period, each subject received oral dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) once a day on Day 1 and Day 10 in the morning (AM dose) and twice a day on Days 2-9 (AM and PM doses) with 240 mL of water. Each AM dose on Day 1-10 were administered following an over night fasting (as of midnight) followed by a breakfast approximately 1 hr later. The PM doses on Days 2-9 were administered in the clinic approximately 10 hr after the AM dose followed by a meal approximately 1 hr later, and food was not allowed for 2 hr prior to the PM dose. On Day 1 and 10, blood samples were collected up to 24 hr after the AM doses, and subjects received standardized meal and beverages on these two days. Each subjects received the same

treatment over two separate periods and the treatment procedure in second treatment period was same as the first treatment period. Two treatment periods were separated by 13-days of washout interval.

Pharmacokinetic profile of esomeprazole following single dose and multiple doses (BID for 10 days) of PN 400 (500 mg naproxen/20 mg esomeprazole) are as following.



Summary of Esomeprazole Pharmacokinetic Parameters (n = 17)

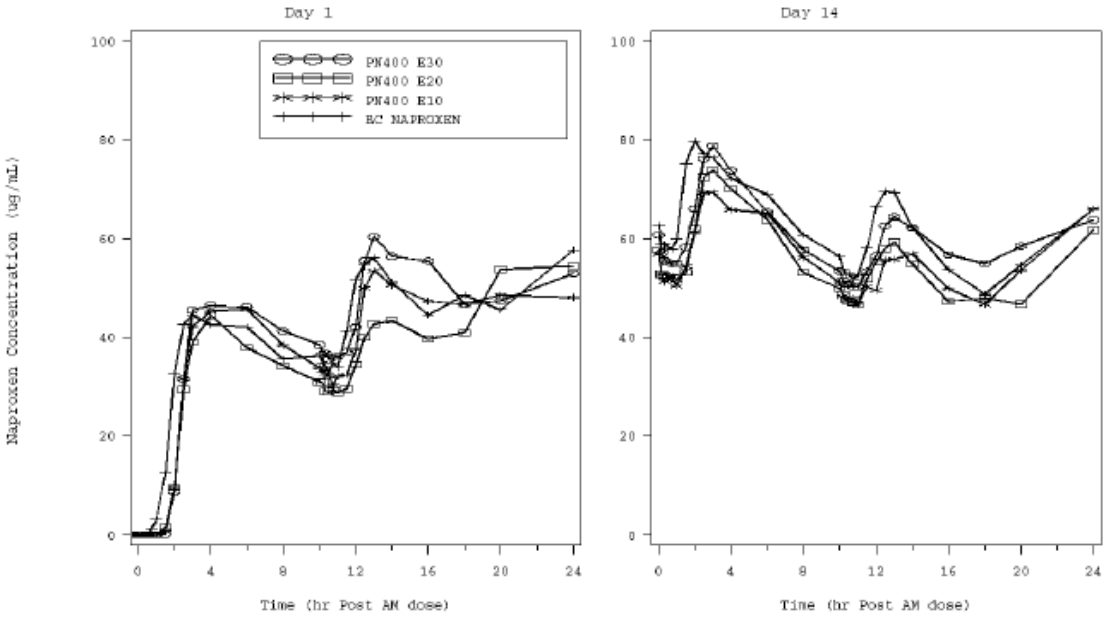
Day	Statistics	Cmax (ng/mL)	AUC0-t (hr*ng/mL)	AUC0-24 (hr*ng/mL)	$t_{½}$ (hr)	AUC0-inf (hr*ng/mL)
1	Mean	383	383	385	0.99	385
	%CV	87	98	97	27	97
10	Mean	1080	2215	2219	1.53	
	%CV	53	74	74	43	

Reviewer's Comments:

Following multiple BID doses of PN 400 for 10 days, esomeprazole concentration was much higher compared to a single dose on day 1 (2.8-fold increase in C_{max} and 5.7-fold increase in AUC). However, the variability in Cmax and AUC of esomeprazole seems to be lower following multiple doses compared to single dose. The Half life of esomeprazole following multiple doses on Day 10 is longer by 0.5 hr compared to single dose on Day 1.

Naproxen pharmacokinetics

Mean Plasma Naproxen Concentration vs. Time Curves for All Treatments on Day 1 and Day 14



Mean (CV%) of Naproxen Pharmacokinetic Parameters by Study Day and Dose Time for Treatment A (PN 400/E30)

Day, dose, N	Cmax (µg/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*µg/mL)	AUC0-24 (hr*µg/mL)	T1/2 (hrs)
Day 1, am N=19	64.7 (27)	5.02 (49)	353 (25)	--	7.68 (16)
Day 1, pm N=20	81.7 (30)	3.75 (92)*	718 (20)*	1070 (15)	14.7 (25)
Day 14, am N=20	87.9 (22)	2.08 (83)	637 (17)	--	11.0 (33)
Day 14, pm N=20	83.4 (35)	3.22 (93)	815 (17)	1452 (12)	13.3 (10)

*N=19;

Mean half-life (CV%) values of Naproxen for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 7.68 hr (16%), 14.7 (25%), 11.0 (33%) , and 13.3 (10%) from 10, 14, 15, and 8 subjects, respectively. Dose accumulation was observed with exposure more than doubled beginning the day 1 pm dose and remained relatively constant after 14 days of administration. The pm half-life was longer than the am half-life for either day 1 or day 14 and was similar between day 1 and day 14.

Mean (CV%) of Naproxen Pharmacokinetic Parameters by Study Day and Dose Time for Treatment B (PN 400/E20)

Day, dose, N	Cmax (µg/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*µg/mL)	AUC0-24 (hr*µg/mL)	T1/2 (hrs)
Day 1, am N=17	64.0 (27)	4.03(39)	354(21)*	--	8.78 (24)
Day 1, pm N=20	74.0 (31)	5.31 (75)	633 (22)&	999 (16)	15.6 (29)

Day 14, am N=19	80.5 (28)	3.63 (64)	601 (24)	--	9.14 (20)
Day 14, pm N=19	73.5 (33)	2.71 (116)	721 (24)	1322 (19)	14.9 (22)

*N=16; &N=18

Mean half life (CV%) values of Naproxen for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 8.78 hr (24%), 15.6 (29%), 9.14 (20%) , and 14.9 (22%) from 12, 8, 13, and 6 subjects, respectively. Similar naproxen pharmacokinetic characteristics were observed following PN 400/EC 20 and PN 400/EC30. The pm dosing did not allow for the am PK profile to complete, thus causing truncation of the am PK profile and shorter am terminal half life.

Mean (CV%) of Naproxen Pharmacokinetic Parameters by Study Day and Dose Time for Treatment C (PN 400/E10)

Day, dose, N	Cmax (µg/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*µg/mL)	AUC0-24 (hr*µg/mL)	T1/2 (hrs)
Day 1, am N=19	61.9 (29)	4.58 (47)	337 (25)	--	8.38 (33)
Day 1, pm N=20	73.3 (30)	4.20 (69)	642 (21)	979 (19)	15.0 (20)
Day 14, am N=19	80.5 (31)	3.17 (74)	599 (27)	--	9.95 (23)
Day 14, pm N=19	69.9 (29)	3.13 (105)	749 (20)	1348 (20)	12.9 (22)

Mean half life (CV%) values of Naproxen for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 8.37 hr (33%), 15.0 (20%), 9.95 (23%) , and 12.9 (22%) from 12, 12, 12, and 5 subjects, respectively.

Reviewer's Comments: Treatments A, B, and C showed similar exposure for naproxen on days 1 and 14, with higher exposure and longer half life on day 14 than on day 1. Even on day 1, the pm dose from each treatment group showed higher exposure. These results demonstrated accumulation of naproxen after multiple days of dosing. The fact that the 10-hour dosing interval is shorter than the half life of naproxen could offer a possible explanation for such outcome. The half life values reported for naproxen do not represent the true terminal half life since there were still substantial plasma naproxen concentrations.

Mean (CV%) of Naproxen Pharmacokinetic Parameters by Study Day and Dose Time for Treatment D (EC Naproxen)

Day, dose, N	Cmax (µg/mL)	Tmax (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*µg/mL)	AUC0-24 (hr*µg/mL)	T1/2 (hrs)
Day 1, am N=17	73.3 (18)	3.76 (57)	411 (19)*	--	9.22 (18)
Day 1, pm N=20	78.3(39)	3.88 (104)	695 (28)&	1089 (22)*	17.1 (51)
Day 14, am N=19	93.6 (21)	2.66 (68)	668 (18)	--	10.5 (30)
Day 14, pm	81.7 (28)	2.80 (121)	808 (19)	1476 (15)	14.5 (41)

N=19
*N=16; &: N=19

Mean half life (CV%) values of Naproxen for Day 1 am, Day 1 pm, Day 14 am, and Day 14 pm, respectively, were 9.22 hr (18%), 17.1 (51%), 10.5 (30%) , and 14.5 (41%) from 13, 9, 13, and 6 subjects, respectively

When comparing treatments A to C with treatment D, it is clear that EC Naproxen showed higher exposure of naproxen than the PN400-CE20 formulation. These results are consistent with the results obtained in study 400-102. PN400-EC30 sometimes had higher Cmax, but other times lower Cmax, than EC naproxen. So were its AUC values.

Summary of Statistical Analysis of Naproxen PK Parameters between Study Days

Day 14 to Day 1 Parameter Ratio	PN 400/E30	PN 400/E20	PN 400/E10	EC Naproxen
$C_{max,am}$ Ratio (90% CI)	1.37 (1.25, 1.51)	1.26 (1.13, 1.42)	1.29 (1.12, 1.49)	1.30 (1.18, 1.42)
$C_{max,pm}$ Ratio (90% CI)	1.02 (0.86, 1.20)	0.98 (0.81, 1.19)	0.96 (0.81, 1.13)	1.10 (0.89, 1.35)
$AUC_{0-10,am}$ Ratio (90% CI)	1.85 (1.64, 2.08)	1.72 (1.56, 1.89)	1.77 (1.51, 2.08)	1.72 (1.60, 1.86)
$AUC_{0-14,pm}$ Ratio (90% CI)	1.14 (1.06, 1.23)	1.16 (1.05, 1.28)	1.16 (1.04, 1.30)	1.19 (1.03, 1.36)
AUC_{0-24} Ratio (90% CI)	1.36 (1.29, 1.43)	1.37 (1.30, 1.45)	1.37 (1.25, 1.50)	1.38 (1.25, 1.53)

The results shown in the table above demonstrated accumulation of naproxen. When comparing treatments A to C with treatment D, it is clear that EC Naproxen resulted in higher exposure of naproxen than PN 400 formulations.

2.2.5 Is the naproxen component of PN-400 bioequivalent to the approved EC-Naproxen (EC-NAPROSYN®) at proposed dosages?

Yes, naproxen component of PN 400 is bioequivalent to the approved EC-naproxen (EC-NAPROSYN®) at both proposed dose of 375 mg and 500 mg.

The sponsor has proposed two dosage strengths (375 mg and 500) for naproxen component of PN-400 which corresponds to the dosage strength of approved product of enteric coated naproxen (EC-NAPROSYN). In this IND application, the sponsor has submitted 3 bioequivalence studies; 1 BE study for 375 mg naproxen dose (Study PN 400-105) and 2 BE studies for 500 mg naproxen dose (Study PN 400-102 and PN 400-114).

<u>Bioequivalence of Naproxen at 375 mg:</u>

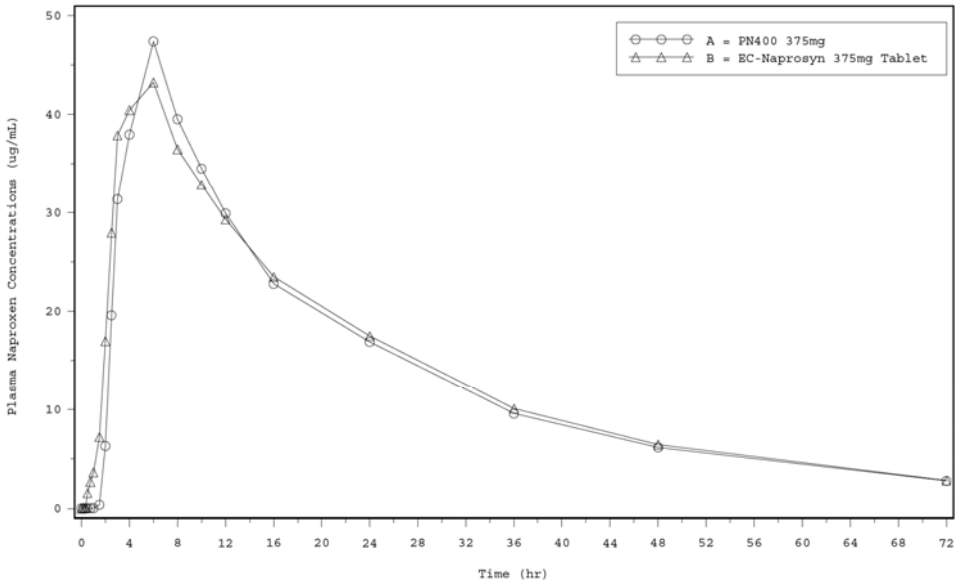
Study PN400-105 is an open-label, randomized, single-center, two-way crossover study to evaluate and compare the relative bioavailability of naproxen following a single oral dose of PN 400 (375 mg Naproxen/20 mg Esomeprazole) versus EC-NAPROSYN® 375 mg in 30 healthy subjects (15 males and 15 females) following an overnight fasting of at least 10 hr. No food was allowed for at least 4 hours post-dose. There was at least 10-days washout interval

between two treatment periods. The main objective of this study was to determine if PN 400 (375 mg naproxen/20 mg esomeprazole) was bioequivalent to EC-ECNAPROSYN® 375 mg in reference to naproxen component. Each treatment dose was administered with 240 mL of water.

The study had equal number of male and female population (15 of each), and mean age was 33.7 (10.4 SD) with the age range of 19-54. The population breakdown by race was 26 White, 3 Black/African American and 1 Asian.

Of 30 enrolled subjects, all of them completed the study as planned. The PK profiles of these two treatments were almost superimposable as demonstrated in below graph and table.

Mean Plasma Naproxen Concentration vs. Time Curves by Treatment



Statistical Analysis of Naproxen (375 mg) BA Parameters between Treatments:

PK Parameter	Geometric LSM Treatment A	Geometric LSM Treatment B		Treatment Comparison A/B
$AUC_{0\text{-}inf}$ (hr*µg/mL)	1044	1069	Geom. LSM Ratio 90% CI	0.977 (0.957, 0.997)
$AUC_{0\text{-}t}$ (hr*µg/mL)	966	991	Geom. LSM Ratio 90% CI	0.974 (0.957, 0.992)
C_{max} (µg/mL)	57.1	55.6	Geom. LSM Ratio 90% CI	1.027 (0.961, 1.096)

Treatment A: PN 400 (375 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 375 mg

Reviewer's Comments:

At 375 mg, the 90% CI for C_{max} and AUC of naproxen are well within the acceptable range of 0.8-1.25. Therefore, naproxen component of PN400 (EC naproxen 375 mg/ IR esomeprazole 20 mg) is bioequivalent to EC NAPROSYN ® 375 mg.

Bioequivalence of Naproxen at 500 mg

- Study PN400-102 is an open-label, randomized, three-way crossover study to evaluate the relative bioavailability of a single oral dose of naproxen 500 mg administered as PN 400 (Naproxen/Esomeprazole), as the naproxen component of PN 400, or as EC-NAPROSYN® in healthy volunteers.

Study 400102 was conducted with the following 3 treatments

Treatment	Study Medication
A	One (1) PN 400 (delayed-release naproxen 500 mg/immediate-release esomeprazole 20 mg) tablet
B	One (1) Naproxen component of PN 400 (similar tablet formulation as PN 400 containing only delayed-release naproxen 500 mg without esomeprazole) tablet
C	One (1) EC-NAPROSYN® 500 mg tablet

All study drugs were administered orally with 240 ml of water following an overnight fast. Tablets were swallowed whole with water and were not to be broken, crushed, or chewed. No food was allowed for at least 4 hours post-dose. .

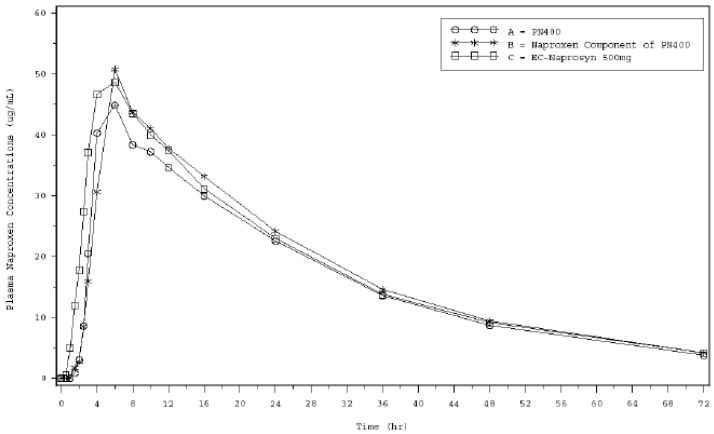
There were 17 males and 19 females aged (mean (SD)) 29 (10.3) years. In terms of race, there were 11 Hispanics and 25 non-Hispanics. Reasons for not completing the study were military obligations (3 subjects) and broken ankle, poor urine sample, and study drug (EC-Naprosyn®) expiration (1 subject each). There were 6 sequences in total as summarized below.

Sequence	Number of Subjects	Treatment Period 1	Treatment Period 2	Treatment Period 3
I	5	A	B	C
II	5	B	C	A
III	5	C	A	B
IV	5	A	C	B
V	5	B	A	C
VI	5	C	B	A

A = PN 400; B = naproxen component of PN 400; C = EC-NAPROSYN®

Treatment periods were separated by at least an 8 day interval for drug washout. According to Naprosyn labeling, "the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. The washout periods of at least 8 days were deemed appropriate.

Median Plasma Naproxen Concentration vs. Time Curves by Treatment:



The plasma concentration/time profiles showed that PN400 had lower exposure than EC-Naprosyn.

Mean (CV%) naproxen pharmacokinetics following oral administration of each treatment

Treatment	Cmax(µg/ml)	AUC0-72 (hr* µg/ml)	AUC0-∞ (hr* µg/ml)	T1/2 (hr)	Tmax (hr)
PN400 (N=32)	57.6 (25)	1178 (19)	1290 (22)	19.3 (18)	7.07 (69)
Naproxen component of PN400 (N=31)	62.6 (21)	1264 (21)	1389 (24)	19.6 (16)	8.13 (77)
EC Naprosyn 500 mg (N=33)	66.6 (20)	1285 (19)	1415 (23)	20.2 (16)	5.78 (79)

PN400 showed similar pharmacokinetic variability as compared to EC-Naprosyn® 500 mg, but lower exposure including AUC and Cmax.

Summary of Statistical Analysis of Naproxen PK Parameters between Treatments

PK Parameter	Geometric LSM			Treatment Comparison	GLSM Ratio	
	A (N=32)	B (N=31)	C (N=33)		Estimate	90% CI
$AUC_{0\text{-}inf}$ (hr*µg/mL)	1284	1363	1383	A/C	0.929	(0.888, 0.971)
				B/C	0.985	(0.942, 1.031)
				A/B	0.942	(0.901, 0.985)
$AUC_{0\text{-}t}$ (hr*µg/mL)	1171	1244	1266	A/C	0.925	(0.884, 0.968)
				B/C	0.983	(0.939, 1.029)
				A/B	0.941	(0.899, 0.985)
C_{max} (µg/mL)	55.0	60.7	65.4	A/C	0.841	(0.768, 0.921)
				B/C	0.928	(0.847, 1.018)
				A/B	0.906	(0.827, 0.993)

A = PN 400, B = Naproxen Component of PN 400, C = EC-NAPROSYN® 500 mg

PN400 had about 16% lower naproxen Cmax than EC-Naprosyn® 500 mg. Comparison of treatments A and B support that esomeprazole did not influence the bioavailability of naproxen. Based on the point estimates for the AUC and Cmax of naproxen, the PN 400 formulation have lower exposure than EC-naprosyn 500 mg and failed to meet the bioequivalence acceptance criterion.

The sponsor commented that less sampling beyond 12 hrs post dose might be problematic and suggested for its calculation of Cmax to exclude those subjects with naproxen tmax equal to or greater than 16 hrs. After such exclusion, the sponsor showed that treatment A was bioequivalent to treatment C.

Summary of Exploratory Statistical Analysis of Naproxen Cmax Values between Treatments Excluding Subjects with Naproxen tmax ≥16 hours

PK Parameter	Geometric LSM			Treatment Comparison	GLSM Ratio	
	A (N=28)	B (N=28)	C (N=31)		Estimate	90% CI
C_{max} (μg/mL)	59.2	62.1	67.1	A/C	0.882	(0.814, 0.955)
				B/C	0.926	(0.854, 1.003)
				A/B	0.953	(0.878, 1.034)

Reviewer's Comments: This study failed to demonstrate bioequivalence for 500 mg naproxen formulated in PN400 as compared to EC Naprosyn 500 mg. The sponsor reasoned that less frequent blood sampling contributed to the failure of demonstrating bioequivalence.

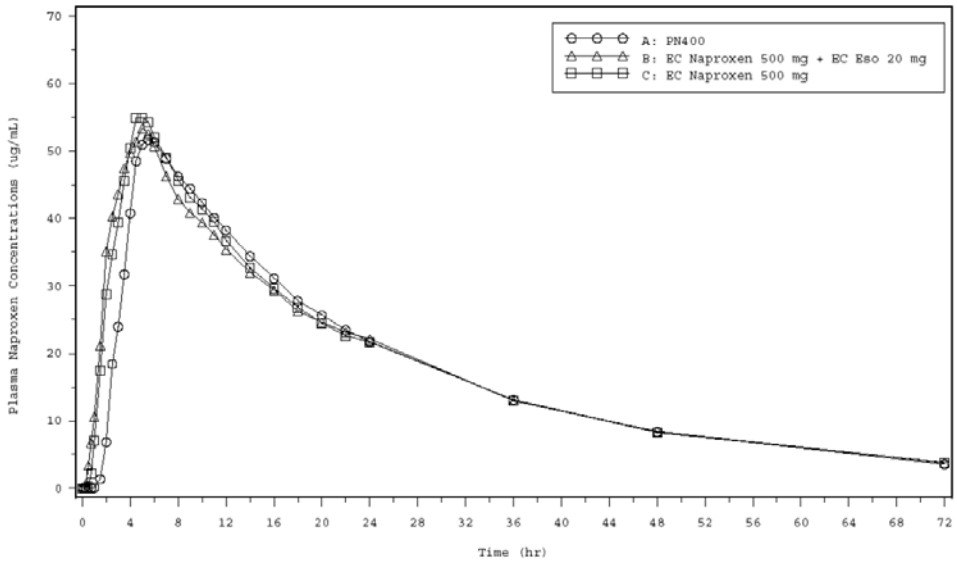
- Study PN400-114 is a randomized, open-label, single-center, 4-way crossover study to evaluate PK and relative BA of naproxen and esomeprazole from single oral dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) in 40 healthy subjects (approximately 20 males and 20 females). The main objective of this study was to determine the bioequivalence of naproxen component in the PN 400 (delayed-release naproxen 500 mg /immediate-release esomeprazole 20 mg) to EC naproxen 500 mg tablet (EC Naprosyn ®). Following an overnight fasting of at least 10 hours, each subject received single oral dose of each of following 3 treatments in crossover study design based on the randomization schedule with 240 mL of water. No food was allowed for at least 4 additional hours after the dose administration. For each treatment group, blood samples were collected at pre-dose, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 36, 48 and 72 hours after the administration of oral dose (31 blood samples/period). There was at least 12-days washout interval between different treatment periods.

Treatment	Study Medication
A	PN 400 (delayed-release naproxen 500 mg / immediate release esomeprazole 20 mg) tablet
B	EC naproxen 500 mg tablet (EC Naprosyn ®) plus EC esomeprazole 20 mg capsule (Nexium®)
C	EC naproxen 500 mg tablet (EC Naprosyn ®)

The study had enrolled equal number of male and female volunteers (20 of each), and mean age was 32.9 (9.5 SD) with the age range of 18-54. The population breakdown by race was 34 white, 5 Black/African American and 1 Asian.

37 out of 40 enrolled subjects completed the study as planned. Of 3 discontinued subjects, 2 of them discontinued for personal reasons and 1 subject withdrew consent.

Mean Plasma Naproxen Concentration vs. Time Curves by Treatment:



Statistical Analysis of Naproxen (500 mg) BA Parameters between Treatments (All subjects)

PK Parameter	**Treatment Comparison** GLSM Ratio (90 % Confidence Interval)		
	A/C	**B/C**	**A/B**
$AUC_{0\text{-}inf}$ (hr*µg/mL)	0.968 (0.937, 1.000)	1.000 (0.968, 1.032)	0.968 (0.938, 1.000)
$AUC_{0\text{-}t}$ (hr*µg/mL)	0.971 (0.942, 1.001)	0.999 (0.970, 1.029)	0.972 (0.943, 1.002)
C_{max} (µg/mL)	0.886 (0.823, 0.954)	0.984 (0.915, 1.058)	0.901 (0.837, 0.970)

Since two subjects had measurable pre-dose naproxen concentrations in 1 or all 3 dose periods that were > 5% of the Cmax, a BE statistical analysis was also performed excluding these two subjects.

Statistical Analysis of Naproxen (500 mg) BA Parameters between Treatments (excluding 2 subjects):

PK Parameter	Treatment Comparison GLSM Ratio (90 % Confidence Interval)		
	A/C	**B/C**	**A/B**
$AUC_{0\text{-}inf}$ (hr*µg/mL)	0.985 (0.960, 1.011)	1.003 (0.978, 1.029)	0.981 (0.956, 1.007)
$AUC_{0\text{-}t}$ (hr*µg/mL)	0.986 (0.963, 1.009)	1.001 (0.978, 1.024)	0.985 (0.962, 1.009)
C_{max} (µg/mL)	0.855 (0.803, 0.911)	0.966 (0.907, 1.028)	0.886 (0.832, 0.944)

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: ECNAPROSYN 500 mg tablet plus NEXIUM 20 mg capsule
Treatment C: EC-NAPROSYN 500 mg tablet

Exclusion of two subjects with measurable pre-dose naproxen concentrations > 5% of C_{max} did not alter statistical analysis for bioequivalence test.

Reviewer's comments:
At 500 mg dose, first BE study for naproxen (PN400-102) has failed the 90% CI of bioequivalence (BE) acceptance criteria for C_{max}. However, in a later study (PN400-114) with more frequent blood sampling (31 vs. 17 samples), the requirements for BE for 500 mg of naproxen for both AUC and C_{max} have met. Therefore, we concluded that PN400 (EC naproxen 500 mg/ IR esomeprazole 20 mg) is bioequivalent to EC NAPROSYN ® 500 mg in terms of naproxen component at 500 mg dose.

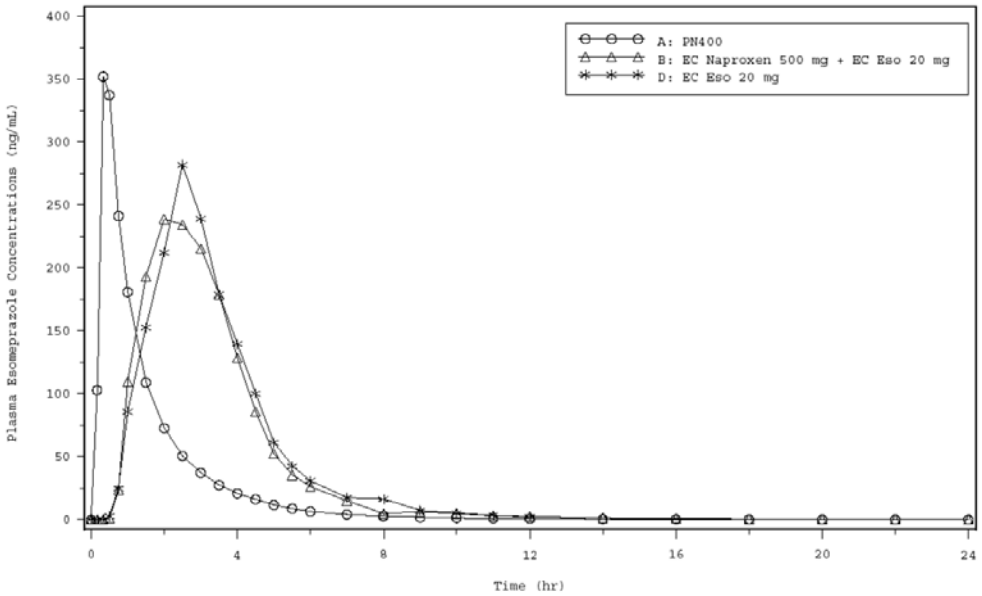
2.2.6 What is the relative bioavailability of esmoeprazole in PN 400 as compared to Nexium?

The extent of esomeprazole bioavailability from single dose of immediate release formulation in PN 400 is about 50% that of enteric coated formulation (EC Nexium®).

Due to instability of esomeprazole in acidic condition in stomach, the commercially available esomeprazole (Nexium®) is available in enteric coated form. However, in this current application, the sponsor proposed to use immediate release formulation for esomeprazole in the combination tablet of PN 400.

In study PN 400-114, the sponsor evaluated the esomeprazole pharmacokinetic profile following a single oral dose administration of either PN 400 (500 mg naproxen/ 20 mg esomeprazole) or EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM) or EC-Esomeprazole capsule (Nexium®) alone to healthy volunteers following overnight fasting of at least 10 hrs. No food was allowed for at least 4 additional hours after the dose administration.

Mean plasma Esomeprazole concentration vs. Time curve by treatment



Summary of Esomeprazole Pharmacokinetic Parameters by treatment:

Treatment	Statistics	C_{max} (ng/mL)	T_{max} (hr)	T_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
A PN 400 (N = 38)	Mean	425	0.51	0.03	465	467	0.971
	%CV	81	49	234	91	91	45
B EC Naproxen +EC Eso (N = 39)	Mean	432	2.50	0.91	801	803	0.945
	%CV	48	54	134	79	79	49
D EC Esomeprazole (N = 39)	Mean	455	2.43	0.87	806	815	0.936
	%CV	40	34	47	78	81	44

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM)
Treatment D: EC-Esomeprazole 20 mg capsule (Nexium®)

In immediate release formulation of esomeprazole in PN 400, Tmax was reached within 0.5 hr versus 2.5 hr in enteric coated formulation in Nexium ®.

Statistical Analysis of Bioavailability Parameters of Esomeprazole between Treatments:

PK Parameter	Treatment Comparison GLSM Ratio (90 % Confidence Interval)		
	A/D	**B/D**	**A/B**
$AUC_{0\text{-}inf}$ (hr*ng/mL)	0.492 (0.424, 0.571)	0.979 (0.843, 1.14)	0.502 (0.432, 0.585)
$AUC_{0\text{-}t}$ (hr*ng/mL)	0.491 (0.422, 0.570)	0.981 (0.843, 1.14)	0.500 (0.429, 0.583)
C_{max} (ng/mL)	0.715 (0.536, 0.955)	0.826 (0.620, 1.10)	0.866 (0.648, 1.16)

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM)
Treatment D: EC-Esomeprazole 20 mg capsule (NEXIUM)

Reviewer' comments:
The extent of esomeprazole bioavailability from single dose of IR formulation in PN 400 is about 50% that of EC formulation (EC Nexium®) in presence and absence of naproxen (based on geometric mean ratio).

2.2.7 Do PN-400 formulations show dose-proportional pharmacokinetics and pharmacodynamics of esomeprazole when referencing EC esomeprazole (20 mg) plus naproxen?

The results presented here are from Study P400-104 with PN 400 tablets. PN 400 tablets contained 500 mg of delayed-release naproxen and 10, 20, or 30 mg of immediate-release esomeprazole (present as 11.1, 22.3, and 33.4 mg esomeprazole magnesium trihydrate salt, respectively), i.e., delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg, delayed-release naproxen 500 mg/ immediate release esomeprazole 20 mg, and delayed-release naproxen 500 mg/ immediate-release esomeprazole 30 mg. These doses of esomeprazole in PN 400 formulations were chosen by picking a lower and a higher dose than the 20 mg esomeprazole dose approved by the Food and Drug Administration (FDA) for ulcer risk reduction. The naproxen tablet strength of 500 mg (Naprosyn®) has been approved by the FDA for the treatment of osteoarthritis and other chronic pain conditions.

The four treatment regimens are listed below. Subjects were dosed with study medication bid, approximately 10 hours apart on Days 1- 9, for a total of 18 doses. Doses were taken 60 minutes prior to breakfast after an overnight fast for the AM dose or 60 minutes prior to dinner for the PM dose for 9 days. The selected timing of dosing of 60 minutes before meals is consistent with Nexium® labeling. Each dose of study drug was administered with 240 ml of water. The sponsor described that tablets were swallowed with water.

Treatment	Treatment Name	Study Medication	Number of Subjects Planned
A	PN 400/E30	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 30 mg) bid	7
B	PN 400/E20	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 20 mg) bid	7
C	PN 400/E10	PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg) bid	7
D	EC E20 + naproxen	EC esomeprazole 20 mg once daily each AM and naproxen 500 mg bid	7

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 (PN400/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)

In treatment regimen D, naproxen tablets were not enteric coated. Products used in treatment D were EC esomeprazole (Nexium®) 20 mg capsules (manufactured by Astra Zeneca) and naproxen (Naprosyn®) 500 mg tablets (b) (4)

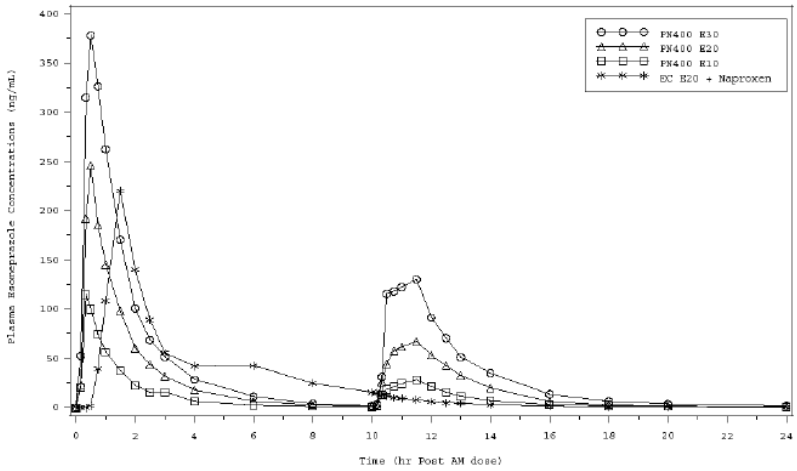
Subjects were randomly assigned to the following four sequences.

Sequence	Number of Subjects	Period 1	Period 2	Period 3	Period 4
I	7	A	D	B	C
II	7	B	A	C	D
III	7	C	B	D	A
IV	7	D	C	A	B

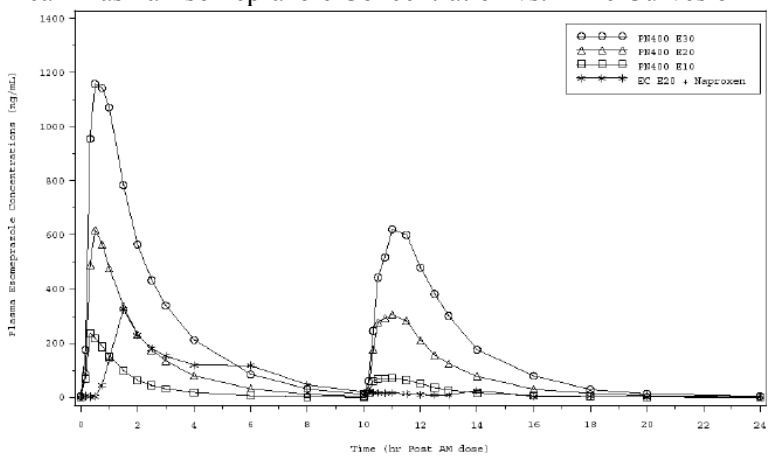
Twenty eight healthy white 25 year olds (F=9, M=19; age: 18-34; mean (SD) height of 178.2 (10.5) cm; mean (SD) weight of 80.7 (15.7) kg) participated in the study. The primary PD endpoint was the percent time of pH > 4.0 on Day 9. Blood samplings were up to 24 hours. Pre-AM dose and the following approximate times post-AM dosing: 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 (pre-PM dose blood sample), 10.17, 10.33, 10.5, 10.75, 11, 11.5, 12, 12.5, 13, 14, 16, 18, 20 and 24 hours.

The plasma concentration/time plots are shown in the following 2 figures.

Mean Plasma Esomeprazole Concentration vs. Time Curves on Day 1



Mean Plasma Esomeprazole Concentration vs. Time Curves on Day 9



On both Days 1 and 9, following the PM dose of PN 400, esomeprazole appeared more slowly in plasma as compared to the AM dose for all three PN 400 treatments, with the first measurable plasma concentration occurring at 20 to 30 minutes post-dose in the majority of subjects. Esomeprazole concentrations on Day 9 were much higher than those on Day 1 following each treatment. The magnitude of differences in esomeprazole concentrations, Day 9 vs. Day 1, increased with the esomeprazole dose level in PN 400.

The AM dose following an overnight fast was absorbed faster and to a greater extent than the PM dose. It is not known what caused this phenomenon. According to the approved label of Nexium, the AUC after administration of a single 40 mg dose of NEXIUM is decreased by 43% to 53% after food intake compared to fasting conditions. NEXIUM should be taken at least one hour before meals. However, for this study, lunch was served 5 hrs after breakfast and food was also not allowed in the afternoon from 2 hours prior to the PM dose until dinner (provided at 60 minutes post PM dose). The reason behind the much lower exposure resulting from the PM dose is unknown. The sponsor did not offer any explanation either. Literature search did not reveal any reports with regard to this observation. The pharmacokinetic characteristics of esomeprazole after each dosing regimen are summarized below.

Mean (CV%) of pharmacokinetic parameters of esomeprazole following PN400/E30

Day, period	Cmax (ng/ml)	AUC0-10,am or	Tmax* (hr)	T1/2 (hr)

		AUC0-14,pm (ng/ml hr)		
1, am	487 (82)	591 (108)	0.5	0.89 (35)
1, pm	187 (132)	388 (137)	1.5	1.11 (62)
9, am	1584 (39)	2779 (45)	0.5	1.26 (25)
9, pm	810 (59)	2066 (53)	1	1.46 (34)

*median, N=28; AUC0-t

Mean (CV%) of pharmacokinetic parameters of esomeprazole following PN400/E20

Day, period	Cmax (ng/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	292 (77)	350 (113)	0.5	0.85 (42)
1, pm	96.6 (104)	206 (141)	1.49	0.99(55)
9, am	715 (52)	1216 (69)	0.5	1.12 (33)
9, pm	438 (73)	919(84)	0.75	1.31 (42)

*median, Day 1: N=28; Day 9:N=27

Mean (CV%) of pharmacokinetic parameters of esomeprazole following PN400/E10

Day, period	Cmax (ng/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	138 (71)	148 (111)	0.33	0.81 (48)
1, pm	35.3 (84)	85.7 (179) [b]	1.5	0.88 (50) [a]
9, am	278 (57)	368 (89)	0.33	0.86 (41)
9, pm	97.6 (136)	223 (134)	1	1.09 (47) [b]

*median; N=27; a:N=25; b. N=26

Across all three PN400/EC dosing regimens on day 1 or day 9, the PM doses resulted in longer Tmax but 1~ 2 fold lower Cmax or AUC as compared to the AM doses. On day 1, the AM doses showed approximately dose proportional increase in Cmax and AUC. So did the PM doses. On day 9, the AM doses showed slightly higher than dose proportional increase in Cmax and AUC. So did the PM doses. For each dosing regimen, the day 9 exposures are 2~ 4 fold higher than the day 1 exposures.

Mean (CV%) of pharmacokinetic parameters of esomeprazole following (EC E20 + Naproxen)

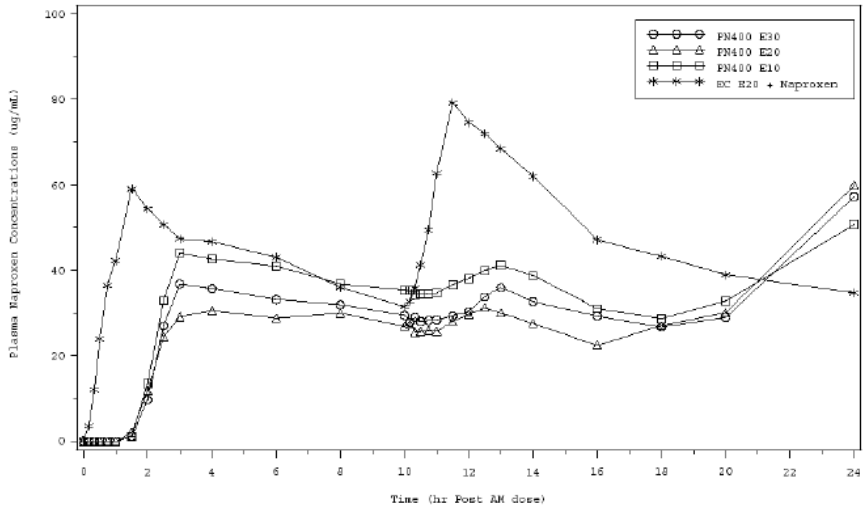
Day	Cmax (ng/ml)	AUC0-10, am (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	282 (66)	540 (60) [b]	1.5	1.1 (44) [b]
9, am	435 (48)	1046 (54)	1.5	1.27 (36) [a]

*median; N=28; a: N=25; b: N=26

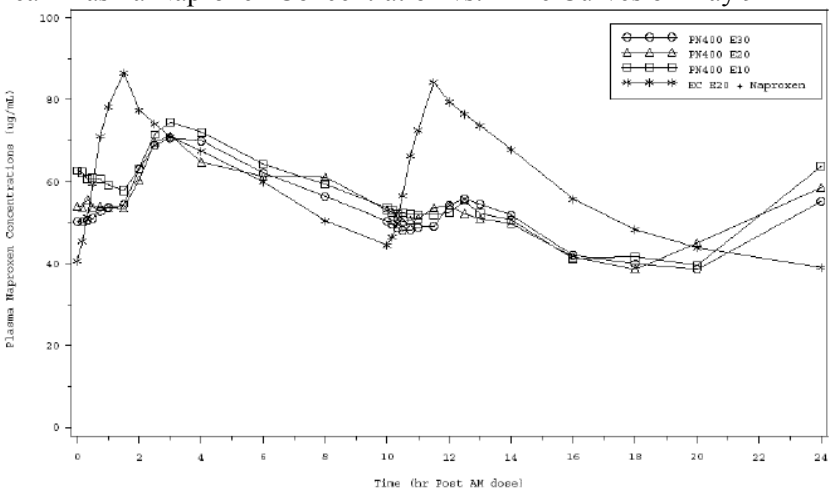
Regardless of what dosing regimens, esomeprazole had higher exposure (Cmax and AUC) on day 9 than on day 1, which is consistent with other proton pump inhibitors in that multiple dosing results in higher exposure. It should be noted that following the day-9 am administration, EC E20+ naproxen resulted in a lower Cmax of esomeprazole but a similar AUC as compared to PN400/E20.

The plasma concentration/time profiles of naproxen following all regimens are shown below.

Mean Plasma Naproxen Concentration vs. Time Curves on Day 1



Mean Plasma Naproxen Concentration vs. Time Curves on Day 9



Naproxen has a half life of 12-17 hours, so it is anticipated that before reaching steady state, twice-a-day administration will result in a higher exposure after the second dose than after the first dose. The results of EC E20 plus naproxen confirmed what is anticipated. The pm PN400/E regimens on day 1 had lower Cmax than their respective am regimens and had second peaks around 24 hrs. Since blood sampling ended at 24 hrs, it is unknown whether the second peaks from the pm dose would reach even higher concentrations past the 24 hr-time. On day 9, naproxen should reach a steady state. The EC E 20 plus naproxen showed slightly lower naproxen exposures following the pm dose than following the am dose on day 9. On day 9, the PN-400/ E regimens had much lower first peaks of naproxen after pm dose than after the am dose, and had the second peaks close to 24 hrs as well.

Based on the results from PN400/E regimens and EC E20 plus naproxen, it is concluded that the pharmacokinetic profiles of both esomeprazole and naproxen from PN400/E regimens were most likely influenced by the performance of sponsor's formulations, not due to the inherent properties of either compound.

The pharmacokinetic characteristics of naproxen following all regimens are shown below.

Mean (CV%) of pharmacokinetic parameters of naproxen following PN400/E30

Day	Cmax (µg/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	48.1 (53)	259 (56)	4	8.52 (25)a
1, pm	68.9 (28)	471 (30)	14	12.1 (30)b
9, am	80.9 (23)	603 (21)	3	9.1(21)c
9, pm	76.2 (23)	648 (20)	10.4	12.3 (27)d

*median; N=28; a. N=17; b.N=21; c. N=26; d. N=24

Mean (CV%) of pharmacokinetic parameters of naproxen following PN400/E20

Day	Cmax (µg/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	44.4 (68)	231 (70)	4	8.75 (33)a
1, pm	71.5 (26)	450 (33)	14	11.8 (28)b
9, am	86.2 (72)	607 (19)	3	9.42 (23)b
9, pm	76.8 (18)	678 (16)	10	11.3 (28)c

*median; Day 1, N=28; Day 9, N=27; a. N=15; b.N=22; c. N=20

Mean (CV%) of pharmacokinetic parameters of naproxen following PN400/E10

Day	Cmax (µg/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	57.0 (31)	310 (35)	4	9.24 (42)a
1, pm	68.6 (26)	508 (29)	10	12.7 (23)b
9, am	87.1 (21)	637 (17)	2.5	9.91 (26)c
9, pm	78.6 (17)	672 (19)	14	10.5 (23)b

*median; N=27; a. N=22; b.N=25; c. N=23

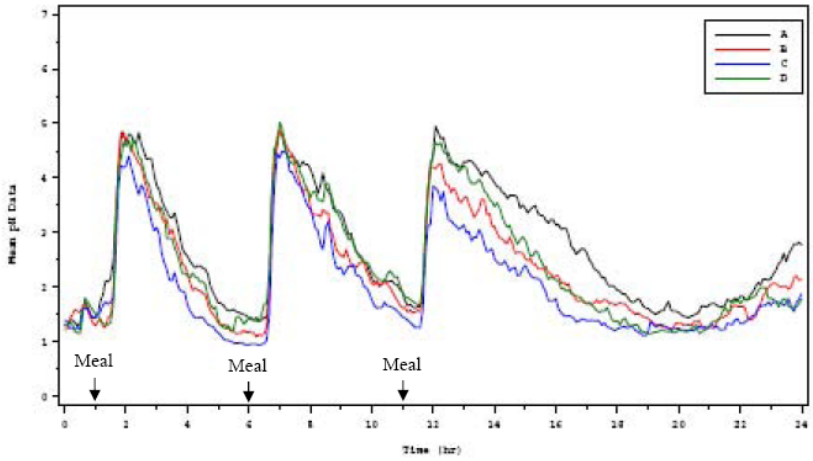
Mean (CV%) of pharmacokinetic parameters of naproxen following EC E20 +naproxen

Day	Cmax (µg/ml)	AUC0-10,am or AUC0-14,pm (ng/ml hr)	Tmax* (hr)	T1/2 (hr)
1, am	65.5 (25)	409 (16)	1.5	8.85 (22)a
1, pm	81.5 (14)	685 (10)	1.5	15.4 (31)
9, am	90 (19)	617 (12)	1.5	9.32 (23)
9, pm	86.5 (13)	769 (10)	1.5	14.4 (17)

*median; N=28; a: N=27

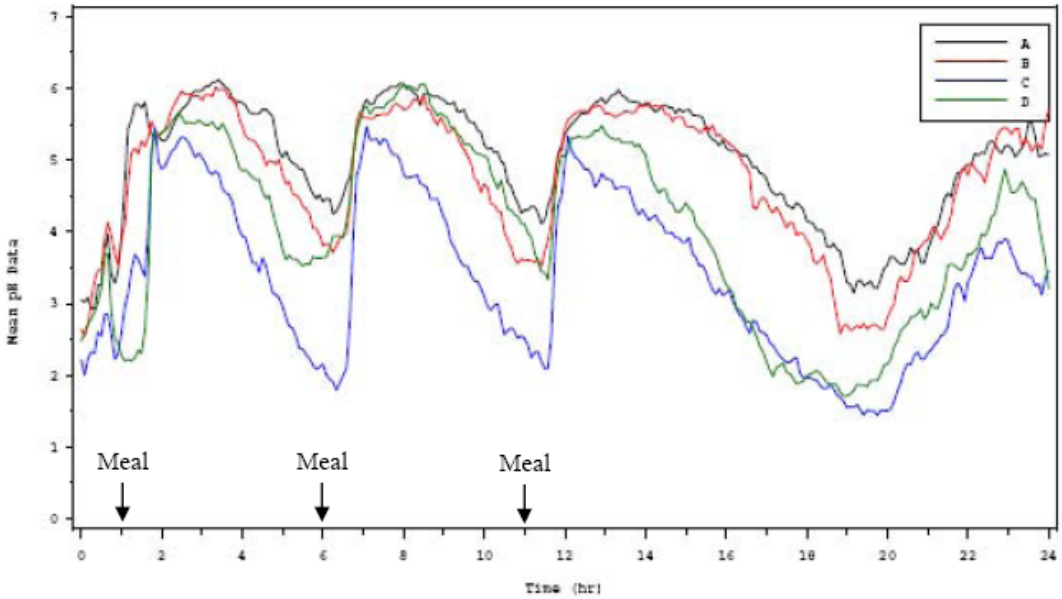
The Cmax and AUC of naproxen, either following am or pm dose, were quantitatively similar across all three regimens of PN400/E30, PN400/E20 and PN400/E10 with slightly higher values following PN400/E10. The Cmax and AUC of naproxen following EC E20 plus naproxen were higher than those following PN400/E30, PN400/E20 or PN400/E10.

Mean Intragastric pH Data over 24 Hours on Day 1



There were obvious pH increases above pH 4.0 throughout the day that were associated with food intake at 1, 6 and 11 hours. The rapid increase in intragastric pH occurred at approximately an hour after each meal for all treatments.

Mean pH Data over 24 Hours on Day 9 – Per-Protocol Population



Treatment: A = PN 400/E30, B = PN 400/E20, C = PN 400/E10, D = EC E20+naproxen

On day 9, PN400/E10 showed lower pH values than before lunch and dinner. For the night time between 14 and 24 hrs, both PN400/E10 and EC E20 + naproxen showed similarly lower pH values than PN400/E30 or PN400/E20. After 9 days of treatment, mean gastric pH values showed a higher degree differentiation among the treatment regimens.

Percent of Time with Intragastric pH Greater than 4.0 – Day 9

Treatment	A PN 400/E30	B PN 400/E20	C PN 400/E10	D EC E20 + Naproxen
	N=25	N=25	N=25	N=25
% Time pH >4.0				
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
%CV	16	18	55	18
Range	49.79 – 95.32	51.76 – 97.61	10.30 – 85.26	40.63 – 75.51
LS Mean (SE)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
	A vs. D	B vs. D	C vs. D	
LS Mean Difference (SE)	19.52 (3.25)	14.23 (3.25)	-16.14 (3.25)	--
95% Confidence Interval	13.04 – 26.01	7.75 – 20.71	-22.26 – -9.66	--

PN 400/E30 = naproxen 500 mg/esomeprazole 30 mg bid
PN 400/E20 = naproxen 500 mg/esomeprazole 20 mg bid
PN 400/E10 = naproxen 500 mg/esomeprazole 10 mg bid
EC E20 + naproxen = EC esomeprazole 20 mg + naproxen 500 mg in AM, naproxen 500 mg in PM. SD = standard deviation; LS = least-squares; SE = standard error; CV = coefficient of variation

The percent time intragastric pH > 4.0 on Day 9 is a primary PD response and increased with esomeprazole dose in the PN 400 regimens. However, there was a greater increase in the primary PD response when esomeprazole dose increased from 10 to 20 mg in PN 400, i.e., from 40.9 to 76.5%. There was only a small increase in intragastric pH > 4.0, from 71.4 to 76.5%, as the esomeprazole dose increased from 20 to 30 mg in PN 400 formulations.

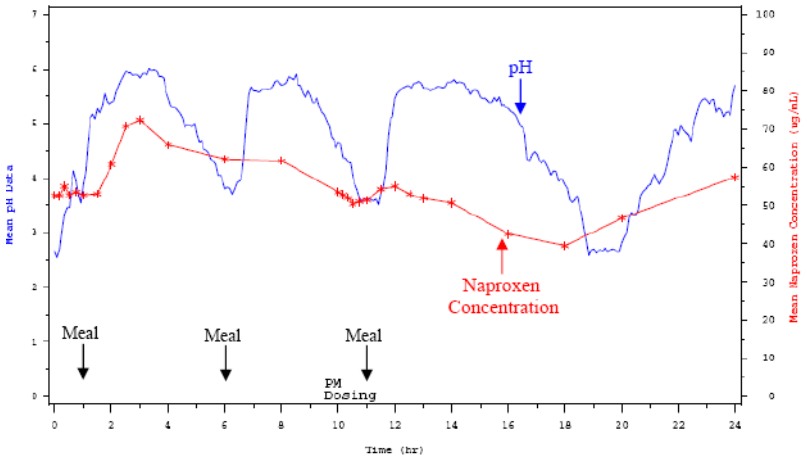
Analysis of percent time of pH > 3.0 and > 5.0 on Day 9 resulted in a similar pattern statistically as that of the primary endpoint of percent time pH > 4 on Day 9 for PP population, with PN 400/E30 and PN 400/E20 showing a greater acid-reducing capacity than EC E20 + naproxen.

The sponsor concluded that
• PN 400/E30 and PN 400/E20 regimens resulted in a higher percent time intragastric pH > 4.0 compared to EC E20 + naproxen given separately, after 9 days of treatment
• PN 400/E30, PN 400/E20 and EC E20 + naproxen treatments were similar in percent time intragastric pH > 4.0 after 1 day of treatment
• PN 400/E10 had the lowest percent time intragastric pH > 4.0 and the highest variability in this response on both Days 1 and 9.
• Based on pH control and low inter-subject variability, PN 400/E20 was selected for studies in subjects at risk for NSAID-associated gastric ulcers.

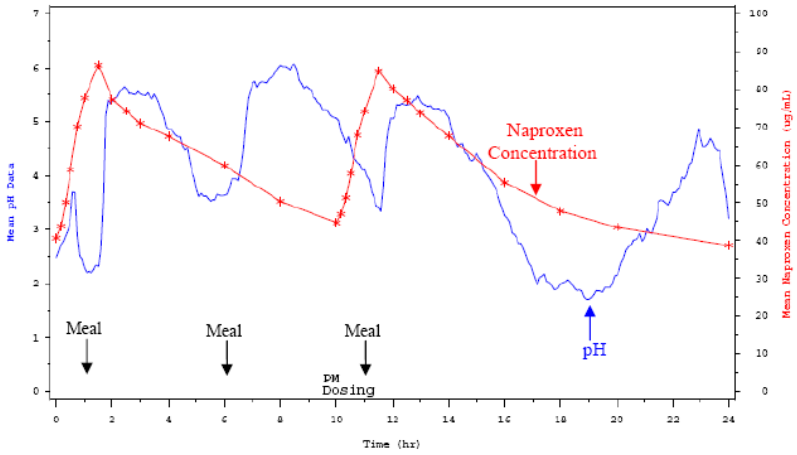
Reviewer's comments: The sponsor's conclusions appear to be reasonable.

Mean pH Data and Mean Naproxen Concentration vs. Time Profiles Over a 24-Hour Period on Day 9

(A) Treatment B (PN 400/E20)

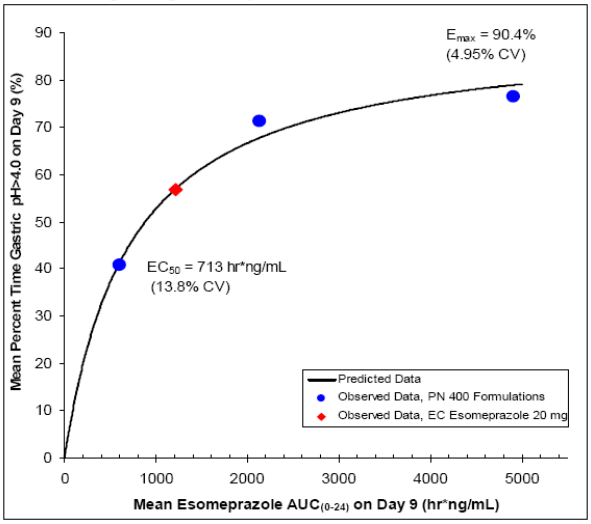


(B) Treatment D (EC E20 + naproxen)



The Cmax values of naproxen following Naprosyn® were higher than following PN-400/E20, while the pH values during the night time reached a lower trough value following Naprosyn® than following PN400/E20.

Correlation of Plasma Exposure to Esomeprazole with Effect on Intragastric pH on Day 9



The Emax was estimated to be 90.4% of time with intragastric pH > 4.0 over the daily interval at steady state. The AUC0-24 value required to achieve half (or 50%) of the maximal response was estimated to be 713 hr*ng/mL. Following PN 400/E20, the PD response had achieved about 80% of the maximal response, which was only slightly less than that (85% of Emax) achieved by PN 400/E30.

The adverse events observed in the study are summarized below.

Clinical Adverse Events Reported by More than 1 Subject (Greater than 4%) on Any Treatment

Body System Adverse Event	A PN 400/E30 N=28	B PN 400/E20 N=28	C PN 400/E10 N=27	D EC E20 + Naproxen N=28
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 adverse event	14 (50)	14 (50)	9 (33)	8 (29)
Gastrointestinal Disorders	9 (32)	8 (29)	8 (30)	5 (18)
Diarrhea	4 (14)	4 (14)	3 (11)	2 (7)
Abdominal distension	2 (7)	2 (7)	2 (7)	2 (7)
Dyspepsia	1 (4)	2 (7)	1 (4)	1 (4)
Abdominal pain upper	3 (11)	0	1 (4)	0
Gastroenteritis, viral	0	0	2 (7)	0
Metabolism and Nutrition Disorders	3 (11)	5 (18)	1 (4)	1 (4)
Iron Deficiency	3 (11)	5 (18)	1 (4)	1 (4)
Nervous System Disorders	4 (14)	1 (4)	0	0
Headache	3 (11)	1 (4)	0	0

PN 400/E30 = naproxen 500 mg/esomeprazole 30 mg bid
PN 400/E20 = naproxen 500 mg/esomeprazole 20 mg bid
PN 400/E10 = naproxen 500 mg/esomeprazole 10 mg bid
EC E20 + naproxen = EC esomeprazole 20 mg + naproxen 500 mg in AM, naproxen 500 mg in PM.

The adverse events reported for PN400/EC formulations were somewhat higher than those reported for EC E20+ naxproxen. Lower adverse event frequencies were observed following PN400/EC 20 than following PN400/EC 30. Based on the pharmacodynamic endpoint of % time intragastric pH>4, the choice PN400/EC 20 with 500 mg naproxen for further clinical trials (studies PN400-301, PN400-302, PN400-303, PN400-304, PN400-307, PN400-309) seems reasonable.

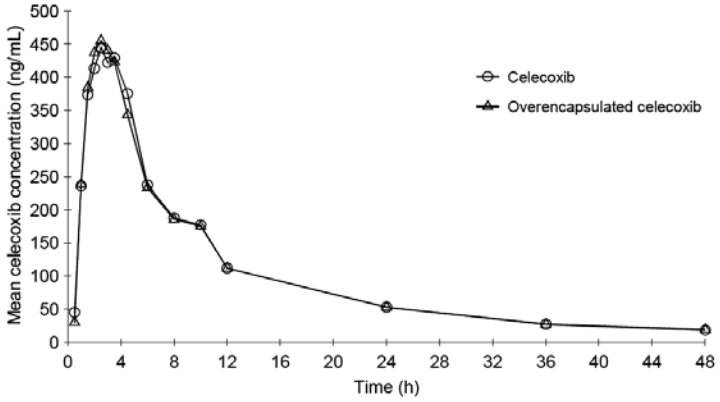
2.2.8 For the non-inferiority study of PN400 with Celecoxib, was the over-encapsulated celecoxib that was used in the study bioequivalent to marketed capsule formulation of celecoxib (Celevrex®)?

Yes, the over-encapsulated celecoxib formulation is bioequivalent to the marketed formulation of celecoxib capsule.

Celebrex® (celecoxib) is a cyclooxygenase (COX)-2 selective NSAID currently marketed for the indications of treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The COX-2 inhibitors are intended to reduce the incidence of GI ulcer. Therefore, celecoxib would be a potential competitor for PN 400. For this reason, the sponsor has conducted a non-inferiority clinical study of PN 400 and celecoxib in treatment of signs and symptoms of osteoarthiritis (PN 400-307 and 309). In order to blind celecoxib in this study, celecoxib was overencapsulated. To unsure the bioequivalence of overencapsulated celecoxib to marketed celecoxib formulation, relative bioavailability of overencapsulated celecoxib as compared to marketed celecoxib formulation was determined in study PN 400-106. PN 400-106 was a randomized, open-label, single-center, 2-way crossover study with 90 healthy volunteers where single oral dose of celecoxib (200 mg) was administered with 240 mL water either as marketed product (Celebrex®) or as over-encapsulated celecoxib following overnight fasting. No food was allowed for at least 4 additional hours after the dose administration. There was at least 7-days of washout interval between different treatment periods. Out of 90 enrolled healthy volunteers, 87 of them completed the study as planned, receiving both treatments. Three subjects discontinued study voluntarily.

The study had 52 male and 38 female with the mean age 32.7 (11.5 SD) and the age range was 18-55. The population breakdown by race was 84 White, 4 Black/African American and 1 Native Hawaiian or other pacific islander.

Mean Celecoxib Plasma Concentration-Time Profiles by Treatments



Summary of Celecoxib Plasma Pharmacokinetic Parameters for Each Treatment:

Treatment/ Statistic	AUC (h*ng/mL)	AUC(0-t) (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2\lambda z}$ (h)	λz (h^{-1})
			Celecoxib			
n	77	87	87	87	87	87
Mean	4673	4621	571.4	2.943	13.60	0.06497
%CV	36.4	41.0	51.4	45.9	52.7	52.7
Geo mean	4385	4203	505.1	2.671	11.93	0.05812
			Overencapsulated Celecoxib			
n	79	87	87	87	86	86
Mean	4632	4598	563.2	NC	13.01	0.06760
SD	1803	2740	298.5	NC	6.948	0.03455
%CV	37.3	41.8	50.6	NC	52.0	52.0
Geo mean	4333	4178	501.0	NC	11.53	0.06016

Statistical Comparison of Key Pharmacokinetic Parameters:

						Comparisons		
Parameter (unit)	**Treatment**	**n**	**Arithmetic Mean**	**Geometric LS Mean**	**95% CI**	**Comparison**	**Ratio**	**90% CI**
AUC (ng*h/mL)	Celecoxib	77	4673	4430	(4095, 4791)			
	Overencapsulated celecoxib	79	4632	4398	(4067, 4756)	Overencapsulated celecoxib / Celecoxib	0.993	(0.960, 1.03)
C_{max} (ng/mL)	Celecoxib	87	571.4	505.0	(455.8, 559.7)			
	Overencapsulated celecoxib	87	563.2	501.3	(452.4, 555.5)	Overencapsulated celecoxib / Celecoxib	0.993	(0.913, 1.08)

Reviewer's comment:
Sponsor's BE study result shows that 90% CI for both AUC and Cmax are within the acceptable range of 0.8-1.25. Therefore, the over-encapsulated celecoxib formulation is bioequivalent to the marketed formulation of celecoxib capsule under fasted conditions.

2.2.9 What is the inter-and intra-subject variability of esomeprazole PK parameters in volunteers, and what are the major causes of variability?

Inter and intra-subject variability of esomeprazole component of PN 400 were assessed in healthy subjects in a phase I, open-label, single-center, 2 treatment period study following single and multiple oral dose administration of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) tablets (study PN 400-111). In each treatment period, each subject received oral dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) once a day on Day 1 and Day 10 in the morning (AM dose) and

twice a day on Days 2-9 (AM and PM doses) with 240 mL of water. Each AM dose on Day 1-10 were administered following an over night fasting (as of midnight) followed by a breakfast approximately 1 hr later. The PM doses on Days 2-9 were administered in the clinic approximately 10 hr after the AM dose followed by a meal approximately 1 hr later, and food was not allowed for 2 hr prior to the PM dose. Each subjects received the same treatment over two separate periods and the treatment procedure in second treatment period was same as the first treatment period. Two treatment periods were separated by 13-days of washout interval.

Both single and multiple doses (steady state) of PN 400 resulted in a very large inter- and intra-subject variability in the esomeprazole PK parameters. The inter-subject variability of esomeprazole was approximately 107-138% for Cmax and 104-120% for AUC following single dose, and 69-96% for Cmax and 114-168% for AUC following multiple dose of PN 400. The intra-subject variability of esomeprazole was 62 % for Cmax and 50% for AUC following single dose and 48% for Cmax and 69% for AUC following multiple doses. Part of the variability in esomeprazole PK following single oral administration of PN 400 is probably due to nature of immediate release formulation of esomeprazole in PN 400 where esomeprazole, which is unstable in acidic environment, is exposed to variable amount of gastric acid in stomach. Part of the variability in esomeprazole PK parameters may be due to its metabolizing enzyme with variable CYP2C19 and CYP3A4 activity. According the Nexium label, CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP 2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2. Of 18 enrolled subjects in this study of PN 400-111, the demographic break down by race was 12 while and 6 black/ African Americans.
Sponsor did not genotype in any of the studies to identify CYP2C19 poor metabolizers in this application..

2.2.10 Was there any food effect on the bioavailability of the drug from the dosage from? What dosing recommendation should be made, if any, regarding the administration of the product in relation to meals or meal types?

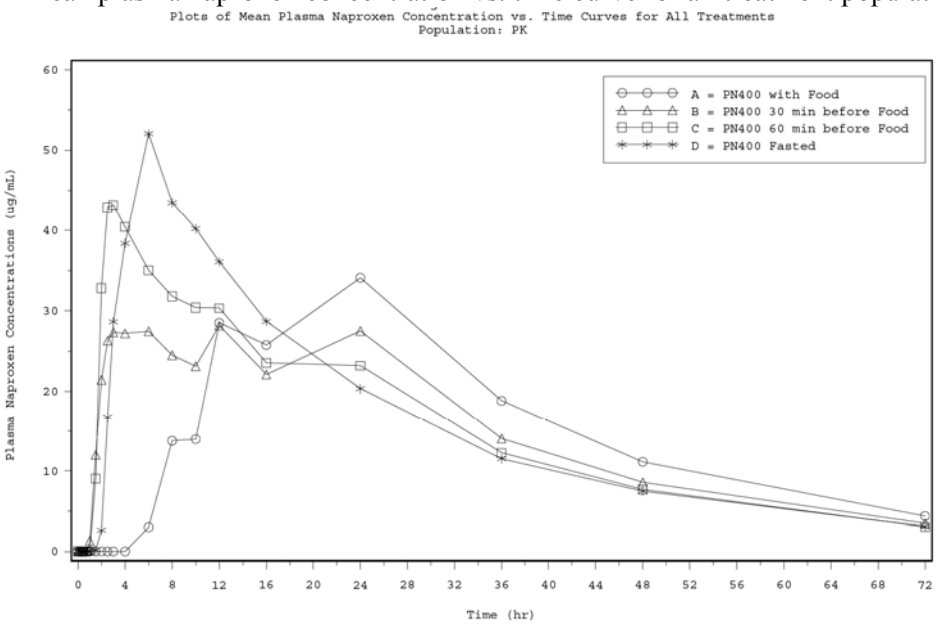
The effect of food and timing of food intake on bioavailability of PN 400 (both naproxen and esomeprazole component) were studied in an open-label, randomized, 4-way crossover, single center study in 24 healthy subjects (study PN 400-103). Each subject received a single dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) in following 4 treatments condition in cross-over study design based on the randomization schedule following a 10-hour overnight fast. The test meals were the standard high-fat, high-calorie breakfast per FDA guideline, containing 800-1000 calories with approximately 50% of the calories from fat. Each dose of study drug was administered with 240 mL of water. Each treatment periods were separated by at least 10-days of washout interval. Of 24 enrolled subjects, 21 completed the study as planned. Of 3 discontinued subjects, two of them were withdrawn due to positive urine drug screens during treatment period 4 check-in and one subject withdrew due a schedule conflicts in treatment period 3. Given the reported half life of naproxen and esomeprazole are 12-17 hr and 1.2-1.5 hr, respectively, according to EC-Naprosyn and Nexium label, 10-days of washout period between different treatments was appropriate. The study method was acceptable from the FDA perspective.

Treatment Regimen

A	Single dose of PN 400 within 5 minutes after completion of a test meal (Fed)
B	Single dose of PN 400 at 30 minutes before the start of a test meal
C	Single dose of PN 400 at 60 minutes before the start of a test meal
D	Single dose of PN 400 followed by an additional 4-hour fast (Fast)

Food Effect on Naproxen Plasma Profile and PK Parameters

Mean plasma naproxen concentration vs. time curve for all treatment population.



Summary of Naproxen PK parameters by treatment:

Treatment	N	Statistics	Cmax (µg/mL)	Tmax (hr)	Tlag (hr)	AUC0-t (hr*µg/mL)	AUC0-inf (hr*µg/mL)	$t_{½}$ (hr)
A PN 400 with Food	22	Mean	55.9	16.5	10.2	1089	1201	17.5
		%CV	27	47	51	13	14	13
B PN 400 30 min before Food	23	Mean	55.5	10.4	5.09	1075	1166	18.1
		%CV	30	78	127	22	22	12
C PN 400 60 min before Food	24	Mean	65.1	6.8	2.87	1093	1178	18.2
		%CV	29	106	158	12	13	12
D PN 400 Fasted	23	Mean	62.4	6.1	2.00	1135	1220	18.8
		%CV	19	55	49	10	12	10

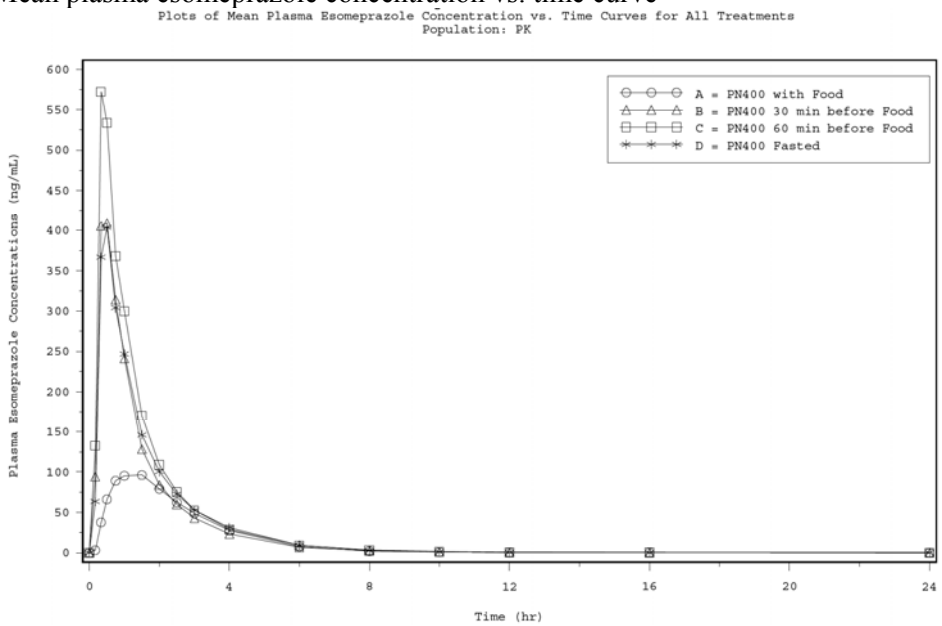
Summary of Statistical analysis of BA Parameters of Naproxen:

PK Parameter	Treatment Comparison GLSM Ratio (90 % Confidence Interval)		
	A/D	**B/D**	**C/D**
$AUC_{0\text{-}inf}$ (hr*µg/mL)	0.977 (0.870, 1.098)	0.907 (0.809, 1.018)	0.964 (0.861, 1.080)
C_{max} (µg/mL)	0.875 (0.733, 1.044)	0.829 (0.696, 0.987)	1.02 (0.860, 1.215)

When PN 400 was given with food, there was a significant delay naproxen absorption (8 hr and 10 hr delay in Tlag and Tmax, respectively), but minimal effect in naproxen Cmax (only 12% decrease in Cmax based on geometric mean ratio). Administration of PN 400 30 minutes prior to food intake had a minor impact on naproxen PK parameters, 17% decrease in Cmax (based on geometric mean ratio) and 3 hr and 4 hr delay in Tlag and Tmax, respectively. When PN 400 was administered 60 min prior to the food, food had no effect on naproxen PK compared to the fasted state. AUC of naproxen for all treatment groups did not change significantly regardless of food intake and timing of food intake.

Food Effect on Esomeprazole Plasma Profile and PK Parameters

Mean plasma esomeprazole concentration vs. time curve



Summary of Esomeprazole PK parameters by treatment

Treatment	N	Statistics	Cmax (ng/mL)	Tmax (hr)	Tlag (hr)	AUC0-t (hr*ng/mL)	AUC0-inf (hr*ng/mL)	t½ (hr)
A PN 400 with Food	22	Mean	125	1.41	0.11	289	304	1.06
		%CV	98	57	135	107	104	43
B PN 400 30 min before Food	23	Mean	491	0.50	0.02	539	542	1.14
		%CV	77	38	264	81	81	49

C PN 400 60 min before Food	24	Mean	637	0.46	0.00	693	696	1.03
		%CV	69	37	.	77	76	46
D PN 400 Fasted	23	Mean	464	0.57	0.01	576	579	1.06
		%CV	80	41	331	80	79	33

Summary of Statistical analysis of BA Parameters of Esomeprazole

	Treatment Comparison GLSM Ratio (90 % Confidence Interval)		
PK Parameter	**A/D**	**B/D**	**C/D**
$AUC_{0\text{-}inf}$ (hr*ng/mL)	0.485 (0.379, 0.621)	0.959 (0.754, 1.22)	1.248 (0.984, 1.58)
C_{max} (ng/mL)	0.249 (0.177, 0.352)	1.089 (0.774, 1.534)	1.503 (1.07, 2.106)

Esomeprazole was rapidly absorbed when PN 400 was administered under fasted state (Tmax of 0.57 hr). When PN 400 was co-administered with food, esomeprazole AUC was decreased by 52%, Cmax by 75% (based on geometric mean ratio) and Tmax was delayed by almost to 1 hr. When PN 400 was administered 30 min before the administration of food, all PK parameters of esomeprazole are comparable to that of under fasted state (geometric mean ratios for AUC and Cmax were close to 1), although the 90% CI for ratio of geometric mean was not within 0.8 to 1.25, probably due to high variability in esomeprazole PK. However, when the PN 400 was administered 60 min before the meal, there was an increase in Cmax by 50% and AUC by 25% compared to fasted state (based on geometric means ratio). The significant reduction in extent of esomeprazole bioavailability from PN 400 when co-administered with food is probably due to that the presence of food prolongs the time in which esomeprazole is exposed to acidic environment of stomach and thus increases the esomeprazole degradation in this acidic environment.

Reviewer's comment:

The extent of naproxen bioavailability from PN 400 is not affected by the co-administration of food and timing of food; however, absorption of naproxen is delayed when PN 400 is administered with food (10 hr delay in Tmax) or 30 min before food intake (4 hr delay in Tmax). In contrary, co-administration of food had a significant effect of extent of esomeprazole bioavailability (52% reduction in AUC and 75% reduction in Cmax) from PN 400, and had a minimum effect on rate of esomeprazole absorption. The finding of this food effect study was consistent with the labeling of individual components of PN 400 (naproxen and esomeprazole) where EC-Naprosyn label indicates "The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (Tmax), but did not affect peak naproxen levels (Cmax)" and Nexium label indicates "The AUC after administration of a single 40 mg dose of NEXIUM is decreased by 43% to 53% after food intake compared to fasting conditions. NEXIUM should be taken at least one hour before meals". This significant food effect on esomeprazole component of PN was taken into consideration in Phase III clinical trial as PN 400 was directed to be taken BID 30-60 min before breakfast or dinner.

When the PN 400 was administered 60 min before the meal, there was an increase esomeprazole exposure (50% increase in Cmax and 25% increase in AUC) compared to fasted

state. However, this increase in esomeprazole exposure does not raise a safety concern since a higher dose of 40 mg esomeprazole (Nexium 40 mg) has already been approved.

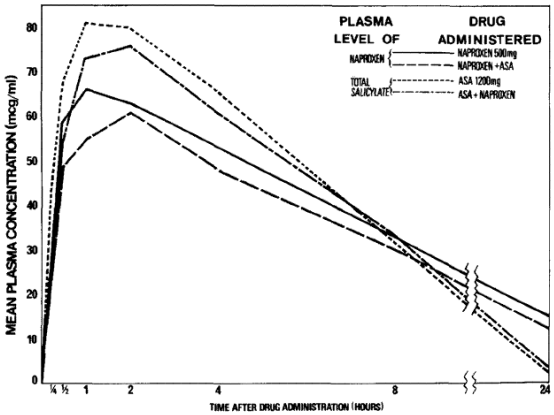
2.2.11 Does aspirin interact with naproxen?

The sponsor submitted a publication from Segre et al on interaction between aspirin and naproxen (Clin Pharmacol and Ther 15(4), 374-379, 1974). Two studies were conducted.

Study 1 involved 6 healthy subjects aged 23 to 40 years (3 males and 3 females) within10% of ideal body weight. Drugs were administered overnight fasting with the sequence of day 1, aspirin (1200 mg) plus naproxen (500 mg); day 4, aspirin (1200 mg); day 7, naproxen (500 mg). The half life of naproxen averaged 15 hrs (approved label), and that of aspirin averaged 5 hrs at the 1 g dose. The washout period of three days is acceptable for both aspirin and naproxen.

Study 2 involved 3 healthy male volunteers weighing 174 to 192 pounds. Drugs were administered following an overnight fast. On day I, the subjects received 500 mg (10 µi) of tritiated naproxen. On day 8, the subjects received 500 mg of 3H naproxcn plus 1200 mg of aspirin.

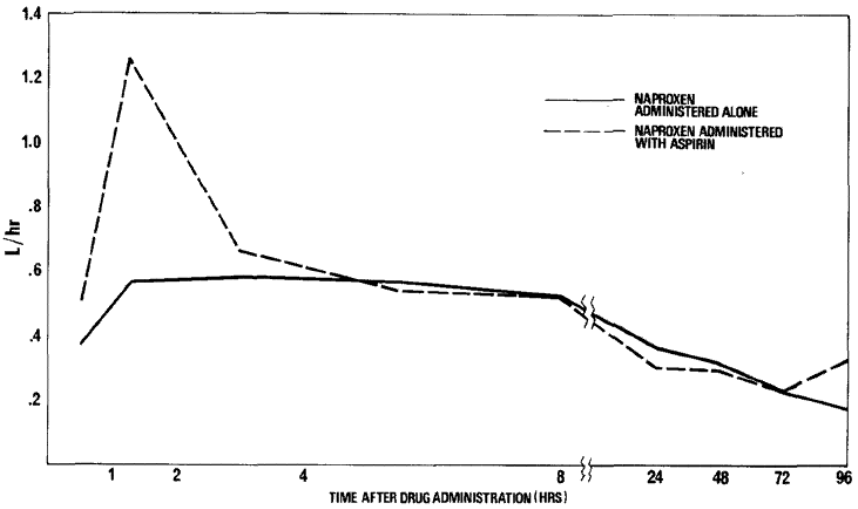
Plasma naproxen and salicylate levels after administration of single doses of each drug separately and together.



Co-administration of aspirin resulted in significantly lower exposure of naproxen (15% lower; p,0.05, 2-tail t test).

Effect of co-administered aspirin on naproxen renal clearance is shown below.

Renal clearance of radioactivity after administration of 3H-naproxen alone (-) or with aspirin (- - -).



Aspirin transiently increased renal clearance of naproxen based on the radio-labeled study, shedding light on decreased exposure of naproxen when aspirin was co-administered as compared to naproxen administered alone. The sponsor further used an in-vitro plasma protein binding study to illustrate the interaction mechanism of aspirin decreasing naproxen exposure and increasing its renal clearance. Aspirin and salicylic acid both reduced plasma protein binding of naproxen in a dose-dependent manner.

Effect of aspirin and salicylic acid on the in-vitro binding of naproxen to human plasma proteins

Salicylate studied and concentration (mM)	*Per cent free naproxen*
None	1.11 ± 0.03
Salicylic acid, 0.4	1.24 ± 0.02*
Salicylic acid, 0.8	1.41 ± 0.04*
Salicylic acid, 4.0	3.09 ± 0.11*
None	1.30 ± 0.07
Aspirin, 0.4	1.48 ± 0.08
Aspirin, 0.8	1.65 ± 0.04†
Aspirin, 4.0	3.19 ± 0.30†

The values represent the mean ± S.E. of 6 (salicylic acid study) or 4 (aspirin study) determinations.

*$p < 0.05$ when compared to per cent free naproxen with no salicylic acid added.

†$p < 0.05$ when compared to per cent free naproxen with no aspirin added.

<u>*The reviewer's comments*</u>: The molecular weight of aspirin is 180g, and that of salicylic acid is 138 g. At 0.4 mM, the gram-based concentration of salicylic acid is 55 microgram/ml, which is within its plasma concentration range shown in the figure above. Increasing the free plasma concentration of naproxen by aspirin could cause a transient increase of naproxen renal clearance when aspirin concentration peaked shortly after administration. This could likely result in decreased exposure of naproxen.

2.3 Extrinsic Factors

2.3.1 What is the metabolic pathway for PN 400?

According the label of approved naproxen (EC-Naprosyn), naproxen is extensively metabolized in the liver primarily by CYP2C9 to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

According to Nexium label, esomeprazole is extensively metabolized in the liver primarily by CYP2C19, which forms the hydroxy and desmethyl metabolites. The remaining metabolism of esomeprazole is via CYP 3A4 which forms the sulphone metabolite

Since naproxen and esomeprazole do not share a common metabolizing CYP enzyme, there is NO known or potential DDI between Naproxen and Esomeprazole

2.3.2 Does the coadministration of naproxen and esomeprazole in PN 400 tablets affect each other's PK profile?

The potential of drug-drug interaction between naproxen and esomeprazpole was evaluated in randomized, open-label, 4-way cross over study (PN 400-114), where naproxen and esomeprazole pharmacokinetic profiles were evaluated in 37 healthy subject following a single oral dose 4 different treatment as describe in table # following overnight fasting of at least 10 hrs.

Treatment	Study Medication
A	PN 400 (delayed-release naproxen 500 mg / immediate release esomeprazole 20 mg) tablet
B	EC naproxen 500 mg tablet (EC Naprosyn ®) plus EC esomeprazole 20 mg capsule (Nexium®)
C	EC naproxen 500 mg tablet (EC Naprosyn ®) (Roche Pharmaceuticals)
D	EC esomeprazole 20 mg capsule (Nexium®) (AstraZeneca)

Results indicated that co-administration of naproxen and esomeprazole do not affect each other PK profile regardless of esomeprazole formulation (IR or EC) suggesting the absence of pharmacokinetic drug-drug interaction between naproxen and esomeprazole components of PN 400.

2.4 General Biopharmaceutics

2.4.1 Is the to-be-marketed formulation identical to the one used for the phase 3 bioequivalence trial?

PN 400 was designed as a multilayer, coordinated delivery tablet formulation combining an immediate-release (non-enteric coated) esomeprazole magnesium layer and a pH sensitive coated naproxen core. According to the sponsor's statement, the commercial formulation for PN 400 (375 mg/20 mg) and PN 400 (500 mg/20 mg) is identical to the

primary stability formulation which was used in the phase 3 clinical studies (sponsor document was provided by Dr. Albert Chen (Biopharm, ONDQA).

2.4.2 What is the to-be-marketed formulation?

Phase 1, Phase 3, and primary stability PN 400 (500 mg/20 mg and 375 mg/20 mg) formulations

Component	Quantity per unit (mg/tablet)			
	Initial Phase 1 500 mg/20 mg	Phase 3 500 mg/20 mg[a]	Primary stability 500 mg/20 mg[b]	Primary stability 375 mg/20 mg[c]

(b) (4)

The excipients used in the 500 mg and 300 mg formulations of PN400/EC20 are approximately dose proportional.

2.5 Analytical Section

2.5.1 What bioanalytical methods were used to assess concentration?

Naproxen concentrations in human plasma were measured by a validate HPLC method with fluorescence detection method.
Since esomeprazole is optically stable and inversion from S to R configuration is minimal in human, plasma esomeprazole concentrations were determined by a validated HPLC/MS/MS method (stereo unselective method) for omeprazole.

Analyte	Method
Naproxen	HPLC/Fluorescence
Omeprazole	HPLC/MS/MS

2.5.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

For naproxen component, the concentration range for standard curve in all studies was 0.1-100 µg/mg. R^2 for naproxen standard curve ranged from 0.9955 to 0.9998.
The standard curve range was appropriate as the naproxen C_{max} in all clinical pharmacology studies ranged 55.5-75.3 µg/m following a single dose and 73.3-93.6 µg/mL following multiple doses administration.

The concentration range for standard curve for esomeprazole in all studies was 1 - 1000 ng/ml. R^2 ranged from 0.9988 to 1.00. The standard curve was appropriate for single dose administration of esomeprazole as Cmax for all clinical pharmacology studies ranges from 125-637 ng/ml following a single dose. Some samples concentrations following multiple dose administration were higher than 1000 ng/ml (Cmax ranged from 468 -1804 ng/ml after multiples doses). Those samples with >1000 ng/ml were appropriately diluted prior to analysis. For the analytical runs which contained diluted subject samples, the appropriate level quality control pool was diluted and analyzed in a similar manner to validate the dilution of study samples.

2.5.3 What are the lower and upper limits of quantification (LLOQ / ULOQ), accuracy and precision?

Analyte	LLOQ	ULOQ	QC precision	QC accuracy
Naproxen	0.1 µg/mL	100 µg/mL	1.91% to 9.62%%	-4.75% to 6.56%
Omeprazole	1.00 ng/mL	1000 ng/mL	1.65% to 6.81%	-0.794% to 2.77%

2.5.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Both naproxen and esomeprazole plasma samples were stored at -20 ^{o}C.

Naproxen long-term stability in human plasma at -20 ^{o}C was established for 1025 days. All naproxen plasma samples were analyzed within 42-104 days.

Esomeprazole long-term storage stability in human plasma at -20 ^{o}C was established for 449 days. All esomeprazole plasma samples were analyzed within 46-116 days.

2.5.5 What is the QC sample plan?

Naproxen 5 QC samples were at concentrations 0.280, 0.800, 3.00, 12.0 and 76.0 µg/mL.
Esomeprazole 5 QC samples were at concentrations 2.60, 8.00, 30.0, 130, and 750 ng/mL.

2.5.6 How was celecoxib detected?

Plasma Celecoxib concentrations were determined by a validated HPLC and LC-MS/MS detection after solid phase extraction method.

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
Celecoxib	HPLC & LC-MS/MS	5.00 ng/mL	2000 ng/mL	5.2% to 7.2%	2.0% to 6.7%

The standard curves for celecoxib ranged from 5.00 to 2000 ng/mL. The standard curve was appropriate as the C_{max} in this study range 563.2-571.4 ng/ml.

The quality controls were at 15, 750, 1500, and 7500 mg/mL concentration.
The samples were stored in -60 to -80 ^{o}C. All samples were analyzed within 150 days of established stability.

3 Detailed Labeling Recommendations

Section 7.2

(b) (4)

The above statement should be revised as follows.

When naproxen is administered with doses of aspirin (>1 gram/day), its protein binding is reduced. The clinical significance of this interaction is not known.

Section 8.3 Nursing Mother

The proposed Vimovo label:

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. (b) (4)

The above statement should be revised as:

The excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. However, omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for esomeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Section 12.2 Pharmacodynamics

Antisecretory Activity

Table 3: Effect on Intragastric pH on Day 9 (N=25)

	Naproxen 500 mg combined with esomeprazole		
	10 mg	20 mg	30 mg
% Time Gastric pH >4[†] LS Mean (SE)	41.1 (3.0)	71.5 (3.0)	76.8 (3.0)
Coefficient of variation	55%	18%	16%

[†] Gastric pH was measured over a 24-hour period

LS Mean (SE) should be placed in the footnote, not inside the table.

Absorption

Naproxen

(b) (4)

This above statement was from study PN400101, and should be revised as follows.

At steady state following administration of VIMOVO twice daily, peak plasma concentrations of naproxen are reached, on the average, 3 hours following both the morning and the evening dose.

Esomeprazole

(b) (4)

[redacted]

This above statement was from study PN400101 and should be revised as follows.

Following administration of VIMOVO twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within, on the average, 0.43 to 1.1 hours following the morning and evening dose on both the first day of administration and at steady state. The peak plasma concentrations of esomeprazole are higher at steady state compared to on first day of dosing of VIMOVO.

Section 12.3
Metabolism

Naproxen:

The proposed Vimovo label:

(b) (4)

[redacted]

The above statement should be revised as:

Naproxen is extensively metabolized in the liver by the cytochrome P450 system CYP2C9 and CYP1A2 to 6-0-desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes.

Section 12.3
Metabolism: The below statement is acceptable.

Consistent with the half-life of naproxen, the area under the plasma concentration time curve increases with repeated dosing of VIMOVO twice daily.

Esomeprazole:

The proposed Vimovo label:

(b) (4)

[redacted]

The above statement should be revised as follows.
The area under the plasma esomeprazole concentration-time curve increases with repeated administration of VIMOVO. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. An increased absorption of esomeprazole with repeated administration of VIMOVO probably also contributes to the time-and dose-dependency.

Excretion
Naproxen

(b) (4)

[redacted]

The above statement should be revised as follows.

Following administration of VIMOVO twice daily, the mean elimination half-life for naproxen is 15 hours following the evening dose, respectively with no change with repeated dosing.

Esomeprazole
Following administration of VIMOVO twice daily, the mean elimination half-life of esomeprazole is approximately 1 hour following both the morning and evening dose on day 1, with a slightly longer elimination half life at steady state (1.2-1.5 hours).

The above statement is acceptable.

Food Effect

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follows.

Administration of VIMOVO together with high-fat food in healthy volunteers does not affect the extent of absorption of naproxen but significantly prolongs t_{max} by 10 hours and decreases peak plasma concentration (C_{max}) by about 12%.

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

Administration of VIMOVO together with high-fat food in healthy volunteers delays t_{max} of esomeprazole by 1 hour and significantly reduces the extent of absorption, resulting in 52% and 75% reductions of area under the plasma concentration versus time curve (AUC) and peak plasma concentration (C_{max}), respectively.

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

Administration of VIMOVO 30 minutes before high-fat food intake in healthy volunteers does not affect the extent of absorption of naproxen but delays the absorption by about 4 hours and decreases peak plasma concentration (C_{max}) by about 17%, but has no significant effect on the rate or extent of esomeprazole absorption compared to administration under fasted conditions.

The sponsor should add following statement:

Administration of VIMOVO 60 minutes before high-fat food intake in healthy volunteer has no effect on the rate and extent of naproxen absorption, however, increases the esomeprazole AUC by 25% and C_{max} by 50% compared to administration under fasted conditions. This increase in esomeprazole C_{max} does not raise a safety issue since the approved dosing regimen of esomeprazole at 40 mg QD would result in a higher C_{max} [see *Dosage and Administration (2)*].

Therefore, VMOVO should be taken at least 30 minutes before the meal.

Special Populations

Geriatric Patients

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

The AUC and Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Race

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

Pharmacokinetic differences due to race have not been studied for naproxen.

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

Approximately 3% of Caucasians and 15 to 20% of Asians lack functional CYP 2C19 enzymes and are called Poor Metabolizers. In these individuals the metabolism of esomeprazole is probably mainly catalyzed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). *Mean peak plasma concentrations were about 60% higher (the sponsor should provide justification for this statement).*

Renal Insufficiency

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow:

Naproxen-containing products, including VIMOVO, are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min)

Gender

The proposed Vimovo label:

(b) (4)

The above statement should be revised as follow: (taken from Nexium label)

The AUC and Cmax values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

4 Appendices

4.1 Individual Study Review

4.1.1 Study PN400-101

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: An Open-Label, Investigator-Blinded, Randomized, Parallel-Group Study to Compare the Gastro-protective Effects of Three PN 400 Dose Combinations (Naproxen 500 mg Combined with Esomeprazole 10, 20, or 30 mg) Using EC Naproxen 500 mg as Control in Healthy Volunteers		
Investigator: Gaetano Morelli, MD		
Study center: MDS Pharma Services, 2350 rue Cohen Street, Saint Laurent, Montreal, Quebec H4R 2N6 Canada		
Publications: none		
Study period: Date first subject enrolled: April 12, 2007 Date last subject completed: May 31, 2007		**Phase of development:** Phase 1

Objectives: The primary objective was to evaluate the efficacy of three PN 400 dose combinations, consisting of a fixed delayed-release naproxen dose combined with different immediate-release esomeprazole doses, in reducing naproxen-associated gastroduodenal injury as determined by combined gastric and duodenal grade 3 or 4 lesions according to Lanza 1988.

Secondary objectives were:

- To evaluate the efficacy of three PN 400 dose combinations, consisting of a fixed delayed-release naproxen dose combined with different immediate-release esomeprazole doses, in reducing naproxen-associated gastroduodenal ulcers
- To assess the pharmacokinetics of esomeprazole on Day 1 and Day 14 in each of the PN 400 treatment groups, and the pharmacokinetics of naproxen on Day 1 and Day 14 in all treatment groups
- To evaluate the safety of each of the treatment arms

The term "gastro-protective" as used in the protocol title reflects the potential ability of PN 400 to reduce naproxen-associated gastroduodenal injury.

Methodology: This was a Phase 1, randomized, investigator-blinded, open-label, parallel-group, active-controlled study conducted in a single center in healthy volunteers. The study consisted of a Screening visit, 12 outpatient visits over a 15-day period and 2 inpatient visits that each lasted approximately 72 hours. Clinical laboratory safety testing was performed at Screening and Day 15 (or early termination). Eligible subjects were admitted to the Phase 1 unit on the evening of Day -2 and underwent a baseline endoscopic examination of the gastric and duodenal bulb mucosa and gastric pH measurement on Day -1.

On Day 1, eligible subjects were randomized to receive one tablet of the following twice-daily (bid) treatments administered 60 minutes prior to breakfast and 60 minutes prior to dinner for 14 consecutive days:

- Treatment A: PN 400 (delayed-release naproxen 500 mg/immediate-release esomeprazole 30 mg); abbreviated as PN 400/E30
- Treatment B: PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 20 mg); abbreviated as PN 400/E20
- Treatment C: PN 400 (delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg); abbreviated as PN 400/E10
- Treatment D: EC naproxen 500 mg; abbreviated as EC naproxen

Just prior to the first dose of study medication on Day 1, serial blood collections for 24-hour pharmacokinetic (PK) assessments were initiated. After the Day 2 morning dosing, subjects were discharged from the unit and asked to return for outpatient dosing bid from the afternoon of Day 2 to the morning of Day 13. In the afternoon on Day 13, subjects were readmitted in the Phase 1 unit for afternoon dosing, in preparation for 24-hour PK blood sampling on Days 14-15 and the final endoscopy on Day 15. Following an overnight fast and prior to receiving the Day 14 morning dose of study drug, a pre-dose PK sample was collected. Following the Day 14 morning dose, sequential blood samples were collected, ending on Day 15 (at 24 hours post Day 14 AM dose). After end-of-study assessments, subjects were discharged from the unit.

Number of subjects (planned and analyzed): 80 subjects (20 per treatment group) were planned, enrolled and treated, 77 completed the study, and data for 80 subjects were analyzed for safety and PK and 79 subjects were analyzed for efficacy.

Diagnosis and main criteria for inclusion: Subjects were males or non-lactating, non-pregnant females 40 to 65 years of age with a body mass index of 19-30 kg/m^2, were *Helicobacter pylori* negative and were generally in good health. Subjects did not have any esophageal, gastric or duodenal mucosal abnormality on baseline endoscopy, a gastric pH >3, nor a history of intolerance or reaction to any proton pump inhibitor or nonsteroidal anti-inflammatory drug.

Test product, dose and mode of administration, batch number: PN 400 combination tablets of naproxen 500 mg/esomeprazole 30 mg (Batch #3056998R) or naproxen 500 mg/esomeprazole 20 mg (Batch # 3056997R) or naproxen 500 mg/esomeprazole 10 mg (Batch # 3056996R) given by mouth bid for 14 days.

Duration of treatment: 14 days

Reference therapy, dose and mode of administration, lot number: EC Naprosyn® 500 mg tablet (naproxen delayed-release tablet), Roche Pharmaceuticals (Lot # E8722, expiration October 2009) given by mouth bid for 14 days.

Criteria for evaluation:

Clinical response: Gastric and duodenal bulb lesions were scored using the Lanza (1988) method: 0 = no visible lesions; 1 = 1 hemorrhage or erosion; 2 = 2-10 hemorrhages or erosions; 3 = 11-25 hemorrhages or erosions; 4 = >25 hemorrhages or erosions or an ulcer.

Pharmacokinetics: Plasma concentration-time profiles of esomeprazole and naproxen over a 24-hour period on Day 1 and Day 14 following the AM and PM doses were determined.

Safety: Safety evaluations included clinical laboratory testing (hematology, chemistry, urinalysis, urine drug screen and pregnancy test for women of childbearing potential), vital signs, physical examination and adverse event assessment.

Endpoints and Statistical Methods:

Sample size: A sample size of 20 subjects per treatment group was considered adequate to detect clinically meaningful differences in gastroduodenal injury between treatments.

Efficacy: The primary endpoint was the percent of subjects with Grade 3 or Grade 4 Lanza (1988) scores in the stomach and duodenal bulb (combined) after 14 days of dosing. The secondary endpoint was the percent of subjects with gastric or duodenal ulcers. For each endpoint, results were compared between each PN 400 and EC naproxen dose group using the Fisher's Exact test. The primary analysis was based on subjects who received at least 75% of all doses of study medication and did not violate the protocol in any major way that would impact the evaluation of efficacy (per protocol population).

Pharmacokinetics:

PK parameters for esomeprazole determined following Treatments A, B, and C and PK parameters for naproxen determined following each of the four treatments included peak plasma concentration (C_{max}) on Days 1 and 14, time to peak plasma concentration (t_{max}) on Days 1 and 14, 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 14, the terminal half-life ($t_{½}$) if possible, following both the AM and PM doses on Days 1 and 14. 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}) was determined on Days 1 and 14. Statistical analysis was performed using Analysis of Variance (ANOVA) to determine the point estimate and 90% CI of the Day 14 to Day 1 ratios for the following parameters for both esomeprazole and naproxen: $C_{max,am}$, $C_{max,pm}$, $AUC_{0-10,am}$, $AUC_{0-14,pm}$, and AUC_{0-24}.

Safety: Adverse events were summarized for each treatment group by system organ class and preferred term. Tabulations and listings of values for vital signs, clinical laboratory tests, and abnormal physical examination findings were produced. Listings of values for each subject were presented with abnormal or out-of-range values for clinical laboratory tests.

SUMMARY

EFFICACY RESULTS: The percent of subjects with a Grade 3 or Grade 4 Lanza score on Day 15 in the stomach and duodenum combined was greater with EC naproxen (74%) than with any of the PN 400 treatments (20-30%). Treatment differences in the distribution of Lanza scores were statistically significant in each pairwise comparison to the EC naproxen treatment ($p \leq 0.01$).

Lanza Scores – Stomach and Duodenum Combined – Day 15 – Per Protocol Population

	PN 400/E30 N=20	PN 400/E20 N=20	PN 400/E10 N=20	EC Naproxen N=19
Lanza Score, n (%)				
0 (no visible lesions)	3 (15.0)	8 (40.0)	2 (10.0)	1 (5.3)
1 (1 hemorrhage or erosion)	1 (5.0)	2 (10.0)	1 (5.0)	0
2 (2-10 hemorrhages or erosions)	12 (60.0)	5 (25.0)	11 (55.0)	4 (21.1)
3 (11-25 hemorrhages or erosions)	4 (20.0)	3 (15.0)	5 (25.0)	5 (26.3)
4 (>25 hemorrhages or erosions, or an ulcer)	0	2 (10.0)	1 (5.0)	9 (47.4)
Subjects with Grade 3 or 4 Lanza (1988) score, n (%)	4 (20.0)	5 (25.0)	6 (30.0)	14 (73.7)
p-value [1] compared to EC naproxen	0.001	0.004	0.010	--

Source: Table 14.2.1.1
PN 400/E30 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 30 mg bid
PN 400/E20 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 20 mg bid
PN 400/E10 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg bid
[1] p-value from Fisher's Exact test

The PN 400/E20 treatment had a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza 1988 Score = 0) compared to all other treatments (range 5.3-15%); the treatment difference between PN 400/E20 and EC naproxen was statistically significant ($p<0.05$). The percent of subjects with at least 1 ulcer on Day 15 in the stomach and duodenum combined was 32% with EC naproxen. No ulcers were found in any subject in the PN 400 treatment. Treatment differences vs EC naproxen in the percent of subjects with at least 1 ulcer on Day 15 in the stomach and duodenum were statistically significant for each pairwise comparison to the EC naproxen treatment ($p<0.01$). An ulcer was defined as a mucosal break of at least 3 mm in diameter with depth.

Presence of Ulcer(s) – Stomach and Duodenum Combined – Day 15 – Per Protocol Population

	PN 400/E30 N=20	PN 400/E20 N=20	PN 400/E10 N=20	EC Naproxen N=19
Subjects with at least 1 gastroduodenal ulcer, n (%)	0	0	0	6 (31.6)
p-value[1] compared to EC naproxen	0.008	0.008	0.008	--

Source: Table 14.2.2
PN 400/E30 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 30 mg bid
PN 400/E20 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 20 mg bid
PN 400/E10 = delayed-release naproxen 500 mg/ immediate-release esomeprazole 10 mg bid
[1] p-value from Fisher's Exact test

PHARMACOKINETIC RESULTS:

Pharmacokinetic data were available from 20 subjects in each treatment on Day 1, and 20 subjects in Treatment A on Day 14, and 19 subjects in each of Treatments B, C, and D on Day 14.

PK parameter estimates of esomeprazole are summarized by treatment as follows.

Treatment	Day/ Dose Time	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	t½ (hr)
A	1 AM	435 (90)	0.50 (0.33-1.00)	594 (83)		0.94 (25)
PN 400/E30	1 PM	457 (120)	0.50 (0.33-1.52)	767 (119)	1361 (99)	1.06 (29)
	14 AM	1804 (26)	0.50 (0.17-1.00)	4161 (32)		1.52 (18)
	14 PM	949 (60)	0.75 (0.33-2.00)	2800 (48)	6961 (36)	1.68 (22)
B	1 AM	339 (84)	0.50 (0.33-0.75)	398 (88)		0.89 (26)
PN 400/E20	1 PM	246 (116)	0.50 (0.33-1.50)	384 (145)	781 (109)	1.06 (33)
	14 AM	1034 (35)	0.50 (0.33-1.00)	1874 (50)		1.24 (35)
	14 PM	468 (81)	0.75 (0.22-4.00)	1120 (73)	2994 (57)	1.48 (36)
C	1 AM	164 (86)	0.33 (0.23-1.00)	234 (153)		0.87 (45)
PN 400/E10	1 PM	159 (139)	0.33 (0.30-2.00)	180 (163)	414 (154)	0.96 (47)
	14 AM	319 (59)	0.50 (0.33-1.50)	535 (93)		1.03 (39)
	14 PM	155 (91)	0.50 (0.33-1.50)	346 (118)	881 (103)	1.24 (52)

Source: Table 14.2.4
Values were mean (%CV) for all parameters, except for tmax, which are median (range).

Esomeprazole was rapidly absorbed from PN 400 formulations, with plasma concentrations measurable as early as 10 minutes post dose in most subjects following both single and repeat doses of PN 400 across esomeprazole dose levels. Esomeprazole concentrations were higher on Day 14 than on Day 1, especially after the AM dose, and this increase was dose related for the PN 400 treatments. The geometric least-squares mean ratios for Day 14 to Day 1 AUC_{0-24} were 7.13, 5.48, and 2.33 following treatment with PN 400/E30, PN 400/E20, and PN

400/E10, respectively. On Day 1 after the AM or PM dose, plasma esomeprazole concentrations increased almost proportionally to the esomeprazole dose in the PN 400 formulations, but on Day 14 plasma esomeprazole concentrations increased more than dose proportionally. The magnitude of this increased bioavailability was dose dependent.

PK prameter estimates of naproxen are summarized by treatment in the table below.

Treatment	Day/ Dose Time	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	t½ (hr)
A	1 AM	64.7 (27)	4.00 (2.50-9.92)	353 (25)		7.68 (16)
PN 400/E30	1 PM	81.7 (30)	3.00 (0.00-13.9)	718 (20)	1070 (15)	14.7 (25)
	14 AM	87.9 (22)	2.50 (0.00-6.00)	637 (17)		11.0 (33)
	14 PM	83.4 (35)	2.50 (0.00-10.0)	815 (17)	1452 (12)	13.3 (10)
B	1 AM	64.0 (27)	4.00 (2.00-8.00)	354 (21)		8.78 (24)
PN 400/E20	1 PM	74.0 (31)	5.01 (0.00-13.9)	633 (22)	999 (16)	15.6 (29)
	14 AM	80.5 (28)	3.00 (0.00-9.92)	601 (24)		9.14 (20)
	14 PM	73.5 (33)	2.50 (0.00-10.0)	721 (24)	1322 (19)	14.9 (22)
C	1 AM	61.9 (29)	4.00 (2.50-9.92)	337 (25)		8.37 (33)
PN 400/E10	1 PM	73.3 (30)	3.00 (0.00-10.0)	642 (21)	979 (19)	15.0 (20)
	14 AM	80.5 (31)	3.00 (0.00-8.00)	599 (27)		9.95 (23)
	14 PM	69.9 (29)	2.50 (0.00-10.0)	749 (20)	1348 (20)	12.9 (22)
D	1 AM	73.3 (18)	2.50 (1.50-9.92)	411 (19)		9.22 (18)
EC naproxen	1 PM	78.3 (39)	2.50 (0.00-13.9)	695 (28)	1089 (22)	17.1 (51)
	14 AM	93.6 (21)	2.50 (0.00-6.02)	668 (18)		10.5 (30)
	14 PM	81.7 (28)	2.00 (0.00-10.0)	808 (19)	1476 (15)	14.5 (41)

Source: Table 14.2.9
Values were mean (%CV) for all parameters, except for tmax, which are median (range).

As expected, absorption of naproxen was delayed following oral administration of PN 400 formulations due to the pH-sensitive coating on the naproxen core which prevents naproxen release in the stomach (i.e., at pH <5). This delay was similar for all 4 treatment groups. The first measurable plasma concentration of naproxen occurred at about 2 hrs post AM dose of each treatment on Day 1, and the median t_{max} values ranged from 2.5 to 5.0 hrs across treatments, dose time and dosing days. There were no differences in the PK profiles of naproxen from any of the PN 400 treatments relative to EC naproxen on both Day 1 and Day 14. Plasma exposure to naproxen increased following repeat doses of PN 400 or EC naproxen, with mean accumulation ratios (Day 14 to Day 1) of 1.36-1.38 for AUC_{0-24}, 1.26-1.37 for $C_{max,,am}$ and 0.96-1.10 for $C_{max,pm}$, respectively. The extent of accumulation following repeat doses of naproxen containing formulations is consistent with the half-life estimates of naproxen and twice daily dosing frequency.

The plasma exposure profiles of esomeprazole and EC naproxen following PN 400 administration are consistent with the sequential delivery design of the tablet, i.e., peak esomeprazole levels precede peak naproxen levels.

SAFETY RESULTS: No serious adverse events were reported. Adverse events occurred in 50%, 40% and 25% of subjects in the PN 400/E30, PN 400/E20 and PN 400/E10 treatment groups, respectively, and in 45% of subjects treated with EC naproxen alone. The most frequent adverse events were abdominal pain (0-10% with PN 400 treatments and 10% with EC naproxen) and diarrhea (0-15% and 5%, respectively). The majority of adverse events were mild. One subject withdrew from the study due to an adverse event, mild skin rashes, assessed as possibly related to study treatment (PN 400/E10).

Laboratory test results were similar among treatment groups for most parameters. Vital sign measurements and physical examination findings in the subjects treated with PN 400 were similar to those in subjects treated with EC naproxen alone.

CONCLUSIONS: The results of this 14 day study in healthy volunteers demonstrate that:

- Use of any of the PN 400 treatments is associated with significantly less gastroduodenal injury compared to EC naproxen, based on lower percentages of subjects with Grade 3 or 4 Lanza (1988) scores ($p \leq 0.01$) and occurrence of gastroduodenal ulcers ($p=0.008$).
- There is a reduction in gastroduodenal injury with all three doses of esomeprazole in PN 400 based on Lanza (1988) scores.
- Esomeprazole was rapidly absorbed from the PN 400 tablets, with plasma concentrations measurable at 10 minutes post dose on Day 1, consistent with the immediate-release nature of esomeprazole formulated in PN 400.
- After repeat dosing of PN 400 treatments, the extent of esomeprazole absorption and plasma exposure to esomeprazole increased substantially. The magnitude of this increased bioavailability was dose dependent.
- Plasma profiles of naproxen were comparable among the three PN 400 treatments and EC naproxen on both Days 1 and 14, indicating that the various doses of esomeprazole in PN 400 did not affect the single- or repeat-dose pharmacokinetics of EC naproxen.
- Since naproxen plasma concentrations were similar among all four treatments, differences in naproxen levels can not explain the reduction in Lanza (1988) scores or the absence of ulcers in the PN 400 treatments compared to EC naproxen.
- The pharmacokinetic profiles of esomeprazole and naproxen from this study showed that the in vivo performance of PN 400 tablets (immediate-release esomeprazole, which reduces gastroduodenal injury and delayed-release naproxen) is consistent with its formulation design of sequential delivery.
- The PN 400/E20 treatment had a higher percentage of subjects with no visible GI lesions (40% of subjects with Lanza 1988 Score = 0) compared to all other treatments (range 5.3-15%); the treatment difference between PN 400/E20 and EC naproxen was statistically significant ($p<0.05$).
- PN 400 and EC naproxen treatments were generally well-tolerated.

4.1.2 Study PN400-102

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

Title of Study: An Open-Label, Randomized, Three-Way Crossover Study to Evaluate the Relative Bioavailability of a Single Oral Dose of Naproxen 500 mg Administered as PN 400 (Naproxen / Esomeprazole), as the Naproxen Component of PN 400, or as EC-NAPROSYN® in Healthy Volunteers

Principal Investigator: Aziz Laurent, MD

Study center: Pharmaceutical Product Development, LP, 7551 Metro Center Dr., Suite 200, Austin, TX 78744

Publications (reference): None

Study period: Date first subject enrolled: 07 March 2008 Date last subject completed: 06 June 2008	**Phase of development:** 1

Objectives:

Primary: To assess and compare the pharmacokinetics and relative bioavailability of a single oral dose of naproxen 500 mg administered in three different formulations: PN 400; the naproxen component of PN 400; and enteric-coated (EC)-NAPROSYN®, in healthy volunteers.

Secondary: To evaluate the safety of the three treatments

Methodology: This was an open-label, randomized, single-center, three-way crossover study to evaluate the pharmacokinetics (PK) and relative bioavailability of a single oral dose of naproxen 500 mg administered as PN 400 (Treatment A), or as the naproxen component of PN 400 (Treatment B), or as EC-NAPROSYN® 500 mg (Treatment C). The study consisted of a Screening Visit, a single dose of study medication, and 4 days of confinement to the Phase 1 facility for PK and safety assessments. Dosing, blood sampling for PK, and safety assessments were repeated on two more occasions to complete the three-way crossover study design. Sequential blood samples for PK assessments were obtained at approximately the following times post-dosing: 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours. Clinical adverse events (AEs) were assessed and concomitant medications were reviewed and recorded as necessary.

Number of subjects (planned and analyzed): A total of 30 subjects were originally planned to be enrolled. A protocol amendment allowed for replacement of subjects that withdrew prematurely. Overall, a total of 36 subjects (17 males and 19 females) were randomized in the study, and 29 subjects (81%) completed evaluations in all three treatment periods of the study. All 36 subjects were included in the PK and Safety analysis populations.

Diagnosis and main criteria for inclusion: Males or non-lactating, non-pregnant females 18 to 55 years of age with a body mass index of 18 to 32 kg/m^2 at screening, who were non-smokers, and generally in good health were enrolled. Subjects with no significant psychiatric conditions, gastrointestinal (GI) disease or gastric surgery and no known allergic reaction, hypersensitivity, or intolerance to non-steroidal anti-inflammatory drugs qualified for entry. Subjects were not to ingest prescription or over-the-counter medications, proton pump inhibitors, H_2 antagonists, anticholinergics, gastric acid-altering compounds, or naproxen-containing products for at least two weeks before the first dosing.

Test product, dose and mode of administration, batch number: One PN 400 (delayed-release naproxen 500 mg/immediate-release esomeprazole 20 mg) tablet (Batch number 3059037R) taken orally. One delayed-release naproxen 500 mg component of PN 400 (the naproxen component is defined as the PN 400 tablet without the esomeprazole component) tablet (Batch number 3059032R) taken orally.

Duration of treatment: Three single-dose treatment periods separated by at least 8 days of drug washout between treatment periods.

Reference therapy, dose and mode of administration, batch number: One commercially available EC-NAPROSYN® 500 mg tablet (Batch number U4711, expiration May 31 2008, Roche Laboratories, Inc.) taken orally.

Criteria for evaluation:

Pharmacokinetic: Plasma concentration vs. time profiles of naproxen were obtained from the analysis of frequent blood samples taken over a 72-hour post-dose period following a single oral dose of the study drug during each treatment period.

Safety: The safety endpoints assessed in this study included physical examinations, vital signs, clinical laboratory values, pregnancy test for female subjects, 12-lead ECG, and AE assessment.

Statistical Methods:

Sample size: Based on the conservative assumption that the within-subject variability is less than 20% in AUC and C_{max} and the expected ratio of means between treatments is 1, a sample size of 30 subjects was estimated to provide at least 90% power to demonstrate bioequivalence at the 0.05 level of significance. Thirty-six (36) subjects were randomized to account for premature subject discontinuation.

Pharmacokinetic analysis: PK parameters were calculated for naproxen using non-compartmental methods. PK endpoints included maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC) from time zero to the last time point with measurable concentration (AUC_{0-t}), AUC extrapolated to infinite time (AUC_{0-inf}), terminal half-life ($t_{½}$), and percentage of extrapolated AUC (% AUC_{extrap}).

Descriptive statistics were calculated for PK parameters of naproxen by treatment. Analysis of variance (ANOVA) was performed on the natural logarithmic (log)-transformed PK parameters $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} to evaluate the relative bioavailability of a single oral dose of naproxen 500 mg administered from three different formulations. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. The geometric least-squares mean (GLSM) ratio between treatments (i.e., Treatment A vs. Treatment C, Treatment B vs. Treatment C, or Treatment A vs. Treatment B) and the corresponding 90% confidence interval (CI) for AUC_{0-inf}, AUC_{0-t} and C_{max} were calculated.

Safety analysis: Adverse Events were coded using MedDRA (Medical Dictionary for Regulatory Activities) for system organ class (SOC) and preferred term. AEs were summarized by SOC and preferred term. Tabulations and listings of values for vital signs, clinical laboratory tests, and abnormal physical examination findings were produced. Listings of values for each subject were produced with abnormal or out-of-range values for clinical laboratory tests.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

A total of 36 subjects were randomized in the study and 29 subjects completed all three treatment periods as planned. Plasma concentration vs. time data of naproxen were available from 32, 31, and 33 subjects receiving Treatments A, B, and C, respectively, which were all included in the PK and statistical analyses. Naproxen PK parameter estimates for each treatment are summarized as follows.

Summary of Naproxen PK Parameters by Treatment

Treatment	Statistics	C_{max} (µg/mL)	t_{max} (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-inf} (hr*µg/mL)	$t_{½}$ (hr)
A PN 400 (N=32)	Mean	57.6	7.07	1178	1290	19.3
	%CV	25	69	19	22	18
	Median	57.9	6.00	1230	1328	18.9
	Min	23.1	3.00	752	868	13.2
	Max	84.4	24.0	1635	1971	29.3
B Naproxen Component of PN 400 (N=31)	Mean	62.6	8.13	1264	1389	19.6
	%CV	21	77	21	24	16
	Median	62.3	6.00	1271	1392	19.6
	Min	34.1	2.00	863	901	13.6
	Max	86.4	36.0	1906	2140	28.3
C EC-NAPROSYN® 500 mg (N = 33)	Mean	66.6	5.78	1285	1415	20.2
	%CV	20	79	19	23	16
	Median	64.3	4.00	1310	1424	19.7
	Min	39.4	1.50	864	902	14.0
	Max	91.5	24.0	1958	2241	27.1

CV = coefficient of variation

Source Data: Table 14.2.2

Naproxen absorption from all three formulations showed delayed release characteristics, with a median lag time of 2.0, 2.1 and 1.5 hrs for Treatments A, B, and C, respectively. Peak plasma naproxen concentration occurred, on average, at 6 hrs after dosing with a PN 400 tablet or the naproxen component of PN 400 tablet, but earlier, at 4 hrs post dose, following dosing with EC-NAPROSYN® 500 mg tablet. There was a wide range of t_{max} values in individual subjects across treatments, ranging from 1.5 to 36 hrs post dose. Several subjects had an unusually prolonged t_{max}, occurring at 16 to 36 hrs post dose, across treatments.

Results of statistical analysis of naproxen AUCs and C_{max} values between treatments using ANOVA are summarized as follows:

Summary of Statistical Analysis of Naproxen PK Parameters between Treatments

PK Parameter	Geometric Least-Squares Mean			Treatment Comparison	GLSM Ratio	
	A	B	C		Estimate	90% CI
$AUC_{0\text{-}inf}$ (hr*µg/mL)	1284	1363	1383	A/C	0.929	(0.888, 0.971)
				B/C	0.985	(0.942, 1.031)
				A/B	0.942	(0.901, 0.985)
$AUC_{0\text{-}t}$ (hr*µg/mL)	1171	1244	1266	A/C	0.925	(0.884, 0.968)
				B/C	0.983	(0.939, 1.029)
				A/B	0.941	(0.899, 0.985)
C_{max} (µg/mL)	55.0	60.7	65.4	A/C	0.841	(0.768, 0.921)
				B/C	0.928	(0.847, 1.018)
				A/B	0.906	(0.827, 0.993)

A = PN 400, B = Naproxen component of PN 400, C = EC-NAPROSYN® 500 mg

Source Data: Table 14.2.3

The 90% CI of the geometric LSM ratio, Treatment B vs. Treatment C and Treatment A vs. Treatment B, for all key PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max}) of naproxen fell within the 0.80 to 1.25 limits to claim bioequivalence.

The 90% CI of the geometric LSM ratio, Treatment A vs. Treatment C, for naproxen $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ fell within the 0.80 to 1.25 limits. However, the lower bound of the 90% CI of the geometric LSM ratio, Treatment A vs. Treatment C, for naproxen C_{max} fell below the limit of 0.80. An exploratory analysis indicated that the somewhat lower naproxen C_{max} value for PN 400 was likely attributable to the unusually prolonged t_{max} in a small number of subjects, perhaps as a result of a low frequency of blood sampling after 12 hours post dose. ANOVA excluding subjects with $t_{max} \geq 16$ hrs showed that the 90% CI of the geometric LSM ratio for naproxen C_{max} for any two treatment comparisons, including Treatment A vs. Treatment C, fell within the limit of 0.80 and 1.25. However, due to these unexplained prolonged t_{max} values, it was decided to obtain bioequivalence (BE) results from another study (PN400-114) to alleviate any questions about BE for the reviewer.

SAFETY RESULTS: No serious AEs were reported. Nineteen AEs were reported by 11 subjects. The majority of AEs were judged to be "mild" in severity (N=18 or 94.7% of AEs), and one was considered "moderate" (ankle fracture; Table 14.3.4) in severity. Six (6) of the AEs were judged to be treatment related and all were "mild" in severity. The incidence of all AEs was 13% with PN 400, 23% with the naproxen component of PN 400, and 9% with EC-NAPROSYN®. Gastrointestinal events were the most frequently reported AEs. No subjects withdrew from the study due to AEs. Laboratory tests, vital signs, and physical examinations did not reveal any safety concerns.

CONCLUSIONS:

- The PN 400 tablet is bioequivalent to its naproxen component of the same formulation in terms of $AUC_{0\text{-}inf}$ and C_{max} of naproxen.
- The naproxen component of PN 400 is bioequivalent to EC-NAPROSYN® 500 mg in terms of $AUC_{0\text{-}inf}$ and C_{max} of naproxen.
- The PN 400 tablet is bioequivalent to EC-NAPROSYN® 500 mg in terms of $AUC_{0\text{-}inf}$ of naproxen.
- All three treatments were generally well tolerated.

4.1.3 PN 400-103: Food Effects on Naproxen and Esomeprazole BA from PN 400

TITLE: An Open-label, Randomized, Four-Way Crossover Study to Evaluate the Effect of Food on the Bioavailability of Naproxen and Esomeprazole from a PN 400 Tablet in Healthy Subjects

STUDY SITE:

Clinical Site: Pharmaceutical Product Development (PPD)
7551 Metro Center Dr., Suite 200, Austin, TX 78744

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

1. To determine the effect of food and the timing of food intake on the bioavailability of naproxen and esomeprazole following a single oral dose of PN 400 in healthy subjects.

2. To evaluate the safety and tolerability of PN 400 under fasting and fed conditions.

STUDY DESIGN:

This study was a randomized, open-label, single-center, 4-way cross-over study with 24 healthy volunteers (approximately 11males and 13 females) to assess the effect of food on relative BA of naproxen and esomeprazole from single oral dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg). Subjects were randomly assigned to one of the 4 treatment sequences indicated in Table-1. Each subject received a single dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) in following 4 treatments condition (Table 2) in cross-over study design based on the randomization schedule following a 10-hour overnight fast. The test meals were the standard high-fat, high-calorie breakfast per FDA guideline, containing 800-1000 calories with approximately 50% of the calories from fat. Each dose of study drug was administered with 240 mL of water. For each treatment, blood samples were collected up to 72-hours after the initial dose. Each treatment periods were separated by at least 10-days of washout interval.

Table-1

Sequence	Number of Subjects	Period 1	Period 2	Period 3	Period 4
I	6	A	D	B	C
II	6	B	A	C	D
III	6	C	B	D	A
IV	6	D	C	A	B

Table-2

Treatment	Regimen
A	Single dose of PN 400 within 5 minutes after completion of a test meal (Fed)
B	Single dose of PN 400 at 30 minutes before the start of a test meal

C Single dose of PN 400 at 60 minutes before the start of a test meal
D Single dose of PN 400 followed by an additional 4-hour fast (Fast)

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 18-55 with Body Mass Index in the range of 18-32 kg/m^2 with negative findings for hepatitis B and C and HIV.

Key exclusion criteria:

- Subject with any gastrointestinal (GI) disease, abnormality or gastric surgery that has potential of interfering with gastric emptying, motility and drug absorption were excluded.
- Subject with personal or family history of an inherited or acquired bleeding disorder.
- Subjects who ingested prescription or over-the-counter medications, monoamine oxidase, inhibitors PPIs, H_2 antagonists, anticholinergics, OTC anti-ulcer medications, gastric acid altering compounds or naproxen-containing products were also excluded.
- Subject with known allergic reaction, hypersensitivity or intolerance to NSAIDs, esomeprazole or other PPI or a significant history of peptic ulcer disease or other acid-related gastrointestinal symptoms were also excluded.

Study Population:

This study had 24 healthy volunteers (11 males and 13 females) enrolled and 21 of them completed the study as planned, receiving all four treatments. Of 3 discontinued subjects, two of them were withdrawn due to positive urine drug screens during treatment period 4 check-in and one subject withdrew due a schedule conflicts in treatment period 3.

Table 3: Subject Enrollment and Disposition – All Randomized Subjects

	Subjects (%) N=24
PK Population	24 (100)
Safety Population	24 (100)
Subjects Completed	21 (88)
Subjects Withdrawn Prematurely	3 (13)
Adverse event	0
Withdrew consent	0
Lost to follow-up	0
Other	3 (13)

Table 4: Demographic Characteristics – ITT Population

	Total Subjects N=24
Age (years)	
n	24
Mean (SD)	34.4 (10.0)
Median	32.5
Range	20-49
Gender – n (%)	
Male	11 (46)
Female	13 (54)
Race – n (%)	
White	20 (83)
Black/African American	4 (17)
Asian	0
Other	0
Ethnicity – n (%)	
Hispanic or Latino	11 (46)
Not Hispanic or Latino	13 (54)
Height (cm)	
n	24
Mean (SD)	170.48 (8.83)
Median	170.50
Range	155.0 – 186.5
Weight (kg)	
n	24
Mean (SD)	77.47 (9.12)
Median	76.85
Range	66.0 – 92.3

Pharmacokinetic Measurements:

For each treatment period, plasma samples were collected at pre-dose, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the administration of oral dose for each treatment groups.

Pharmacokinetic parameters (C_{max}, t_{max}, t_{lag}, AUC_{0-t}, AUC_{0-inf}, $t_{½}$, $\%AUC_{extrap}$) of naproxen and esomeprazole in individual subjects were determined by non-compartmental method from the plasma concentration vs. time profiles with WinNonlin Professional software.

Analysis of variance (ANOVA) was performed on the logarithmic (log)-transformed PK parameters AUC_{0-t}, AUC_{0-inf} and C_{max} to evaluate the effect of food on relative bioavailability of esomeprazole and naproxen between treatments. The ANOVA model included sequence, period and treatment as fixed effects, and subject within sequence as a random effect. The geometric least-squares means ratios between treatments and the associated 90% confidence intervals for AUCs and C_{max} were calculated.

RESULTS:

Of 24 enrolled healthy subjects, 21 subjects completed all treatment periods. 22, 23, 24, and 23 subjects completed treatment A, B, C and D, respectively.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory values, pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse even (AE)t assessments. According to the sponsor, there were no serious adverse events or wdeithdrawals due to adverse events. All of the reported adverse events were mild.

Table 9: Overview of Adverse Events – Safety Population

Treatment	A PN 400 with meal	B PN 400 30 minutes before meal	C PN 400 60 minutes before meal	D PN 400 followed by 4-hour fast
	N=22	N=23	N=24	N=23
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 adverse event	2 (9)	3 (13)	2 (8)	3 (13)
Subjects with at least 1 serious adverse vent	0	0	0	0
Deaths	0	0	0	0
Withdrawals due to adverse events	0	0	0	0

Table 10: Clinical Adverse Events – Safety Population

Treatment	A PN 400 with meal	B PN 400 30 minutes before meal	C PN 400 60 minutes before meal	D PN 400 followed by 4-hour fast
	N=22	N=23	N=24	N=23
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 adverse event	2 (9)	3 (13)	2 (8)	3 (13)
Respiratory, thoracic and mediastinal disorders	0	0	2 (8)	1 (4)
Nasal congestion	0	0	2 (8)	0
Pharyngolaryngeal pain	0	0	2 (8)	0
Epistaxis	0	0	0	1 (4)
Eye disorders	0	1 (4)	1 (4)	0
Eye pruritus	0	0	1 (4)	0
Eye swelling	0	1 (4)	0	0
Gastrointestinal disorders	1 (5)	0	0	1 (4)
Dry mouth	1 (5)	0	0	0
Nausea	0	0	0	1 (4)
General disorders and administration site conditions	0	1 (4)	0	0
Fatigue	0	1 (4)	0	0
Injury, poisoning and procedural complications	0	1 (4)	0	0
Contusion	0	1 (4)	0	0
Musculoskeletal and connective tissue disorders	1 (5)	0	0	0
Musculoskeletal pain	1 (5)	0	0	0
Psychiatric disorders	0	1 (4)	0	0
Libido increased	0	1 (4)	0	0
Reproductive system and breast disorders	0	0	0	1 (4)
Dysmenorrhea	0	0	0	1 (4)

REVIEWER'S COMMENTS:

- Co-administration of high-fat meal with PN 400 delayed naproxen absorption (longer t_{max}) and slightly reduced the rate of absorption (lower C_{max}); however it did not affect the extent of naproxen bioavailability (AUC).

- Co-administration of high-fat meal with PN 400 significantly reduced extent of esomeprazole bioavailability from PN 400 (75% reduction in reduction in C_{max} and 52 % reduction in AUC), however had minimum effect on rate of esomeprazole absorption (1 hr delay in t_{max})

- When PN 400 was administered 30 or 60 min prior to a high-fat meal, food had a minimal effect on both naproxen and esomeprazole absorption.

4.1.4 Study PN400-104

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

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 3056996R, 3056997R and 3056998R 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 ($t^{1}/_{2}$), 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}, $t^{1}/_{2}$, 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.

SUMMARY

PHARMACODYNAMIC RESULTS:

Primary Pharmacodynamic Endpoint

On Day 9, both PN 400/E30 and PN 400/E20 treatments resulted in a greater percent time with intragastric pH > 4.0 than treatment with EC E20 + naproxen. PN 400/E10 had the lowest percent time with intragastric pH > 4.0 and was also the most variable treatment as evidenced by the high %CV in the in-text table below.

Percent Time of pH Greater than 4.0 – Day 9 – Per-Protocol Population

	A PN 400/E30 N=25	B PN 400/E20 N=25	C PN 400/E10 N=25	D EC E20 + naproxen N=25
% Time of pH > 4.0				
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
% Coefficient of variation	16	18	55	18
Range	49.79 – 95.32	51.76 – 97.61	10.30 – 85.26	40.63 – 75.51
LS Mean (SD)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
LS Mean Difference (SE)	A vs. D 19.52 (3.25)	B vs. D 14.23 (3.25)	C vs. D -16.14 (3.25)	--
95% Confidence Interval	13.04 – 26.01	7.75 – 20.71	-22.26 – -9.66	--

PN 400/E30 = naproxen 500 mg/esomeprazole 30 mg bid
PN 400/E20 = naproxen 500 mg/esomeprazole 20 mg bid
PN 400/E10 = naproxen 500 mg/esomeprazole 10 mg bid
EC E20 + naproxen = EC esomeprazole 20 mg + naproxen 500 mg in AM, naproxen 500 mg in PM.
SD = standard deviation; LS = least-squares; SE = standard error; CV = coefficient of variation
Source: Table 14.2.1.1

Secondary Pharmacodynamic Endpoint

On Day 1, the LS mean percent time intragastric pH > 4.0 ranged from 13% with PN 400/E10 to 28% with PN 400/E30. Treatment differences compared to EC E20 + naproxen were small. Only PN 400/E30 (28%) had a statistically significant, greater percent time with pH > 4.0 compared to EC E20 + naproxen (21%).

PHARMACOKINETIC RESULTS

PK analysis was performed for esomeprazole and naproxen plasma concentration vs. time data from 28 subjects completing PN 400/E30 and EC E20 + naproxen treatments and 27 subjects completing PN 400/E10 treatment on Days 1 and 9; and 28 and 27 subjects completing PN 400/E20 treatment on Day 1 and Day 9, respectively.

Esomeprazole Pharmacokinetic Parameters

Treatment	Day/ Dose Time	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	$t^{1/2}$ (hr)
A	1	487	0.50	591		0.892
	AM	(82)	(0.33-1.50)	(108)		(35)
PN 400/E30	1	187	1.50	388	978	1.11
	PM	(132)	(0.33-4.00)	(137)	(115)	(62)
	9	1584	0.50	2779		1.26
	AM	(39)	(0.17-1.50)	(45)		(25)
	9	810	1.00	2066	4911	1.46
	PM	(59)	(0.33-8.00)	(53)	(42)	(34)

B	1	292	0.50	350		0.846
	AM	(77)	(0.20-1.50)	(113)		(42)
PN 400/E20	1	96.6	1.49	206	556	0.994
	PM	(104)	(0.33-3.00)	(141)	(119)	(55)
	9	715	0.50	1216		1.12
	AM	(52)	(0.17-1.50)	(69)		(33)
	9	428	0.75	919	2134	1.31
	PM	(73)	(0.33-3.00)	(84)	(74)	(42)
C	1	138	0.33	148		0.810
	AM	(71)	(0.17-3.10)	(111)		(48)
PN 400/E10	1	35.3	1.50	85.7	237	0.878
	PM	(84)	(0.33-3.00)	(179)	(133)	(50)
	9	278	0.33	368		0.860
	AM	(57)	(0.17-1.00)	(89)		(41)
	9	97.6	1.00	223	602	1.09
	PM	(136)	(0.33-2.00)	(134)	(103)	(47)
D	1	282	1.50	540	580	1.09
EC E20	AM	(66)	(1.00-16.0)	(60)	(67)	(44)
+	9	435	1.50	1046	1212	1.27
naproxen	AM	(48)	(1.00-14.0)	(54)	(47)	(36)

Values are mean (% CV) for all parameters, except for t_{max}, which are median (range).
Source: Table 14.2.6

Following oral administration of PN 400, esomeprazole was rapidly absorbed with plasma esomeprazole concentrations measurable at 10 minutes after the AM dose, and at 20-30 minutes after the PM dose. Plasma esomeprazole concentrations after the PM dose were lower than those after the AM dose on both days. C_{max} and AUCs of esomeprazole increased nearly dose proportionally after the AM dose on Day 1, but more than dose proportionally after the PM dose on Day 1 and both the AM and PM doses on Day 9. Esomeprazole concentrations were much higher on Day 9 than on Day 1 for each PN 400 treatment, presumably reflecting the increased intragastric pH and concurrent reduced gastric acid degradation of esomeprazole after repeat dosing. The geometric least-squares mean AUC_{0-24} ratios, Day 9 to Day 1, were 7.13, 4.10, and 2.26 for treatment with PN 400/E30, PN 400/E20, and PN 400/E10, respectively.

Following EC E20 + naproxen treatment, esomeprazole absorption was delayed, as expected from an EC formulation, with the first measurable concentration at 0.5 to 1.5 hrs. post dose. To evaluate the effect of the immediate-release formulation of esomeprazole from PN 400 with EC E20, the PK parameters from PN 400/E20 and EC E20 + naproxen treatments were compared. On Day 1, esomeprazole $C_{max,am}$ mean values were approximately equal for the PN 400/E20 and EC E20 + naproxen treatments (292 and 282 ng/ml, respectively). In line with the expectation that the immediate-release esomeprazole would be more susceptible to gastric acid degradation than the EC formulation, the AUC_{0-10} mean values on Day 1 from the PN 400/E20 treatment were approximately two-thirds that of EC E20 + naproxen treatment (350 vs. 520 hr·ng/ml, respectively). By Day 9 however, the esomeprazole AUC_{0-10} from the immediate-release formulation was greater than that from EC formulation (1216 vs. 1046 hr·ng/ml, respectively) and $C_{max,am}$ from the immediate-release formulation was almost double that from the EC formulation (715 vs. 435 ng/ml, respectively). These data demonstrate that, following repeat PN 400 dosing, its immediate-release esomeprazole may not be as susceptible to gastric acid degradation as was originally believed.

Naproxen Pharmacokinetic Parameters

Treatment	Day/ Dose Time	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	t½ (hr)
A	1	48.1	4.00	259		8.52
	AM	(53)	(2.00-10.0)	(56)		(25)
PN 400/E30	1	68.9	14.0	471	730	12.1
	PM	(28)	(0.50-14.0)	(30)	(32)	(30)
	9	80.9	3.00	603		9.17
	AM	(23)	(0.00-8.00)	(21)		(21)
	9	76.2	10.4	648	1251	12.3
	PM	(23)	(0.00-14.0)	(20)	(16)	(27)
B	1	44.4	4.00	231		8.75
	AM	(68)	(2.00-10.0)	(70)		(33)
PN 400/E20	1	71.5	14.0	450	680	11.8
	PM	(26)	(0.00-14.0)	(33)	(36)	(28)
	9	86.2	3.00	607		9.42
	AM	(22)	(0.00-8.05)	(19)		(23)
	9	76.8	10.0	678	1275	11.3
	PM	(18)	(0.00-14.0)	(16)	(15)	(28)
C	1	57.0	4.00	310		9.24
	AM	(31)	(2.00-10.0)	(35)		(42)
PN 400/E10	1	68.6	10.0	508	819	12.7
	PM	(26)	(0.00-14.0)	(29)	(21)	(23)
	9	87.1	2.50	637		9.91
	AM	(21)	(0.00-8.00)	(17)		(26)
	9	78.6	14.0	672	1309	10.5
	PM	(17)	(1.50-14.0)	(19)	(15)	(23)
D	1	65.5	1.50	409		8.85
	AM	(25)	(0.75-6.00)	(16)		(22)
EC E20	1	81.5	1.50	685	1094	15.4
+	PM	(14)	(0.50-2.50)	(10)	(12)	(31)
naproxen	9	90.0	1.50	617		9.32
	AM	(19)	(0.50-4.00)	(12)		(23)
	9	86.5	1.50	769	1387	14.4
	PM	(13)	(0.75-4.00)	(10)	(10)	(17)

Values are mean (%CV) for all parameters, except for t_{max}, which are median (range).
Source: Table 14.2.11

Following oral administration of PN 400, the first measurable naproxen concentrations occurred at about 2 hrs. post AM dose on Day 1. Plasma exposure to naproxen was comparable among the three PN 400 treatments. Following repeated doses of PN 400, the Day 9 to Day 1 naproxen concentration ratio was consistent with the expected accumulation based on the half-life estimates of naproxen. The variability in naproxen AUC between AM and PM doses was less on Day 9 than on Day 1, reflecting that naproxen levels are approximately at steady state with repeat dosing. C_{max} values were somewhat more variable between the AM and PM doses on Day 1 compared to Day 9, with mean AM levels being lower than mean PM levels for all treatments on Day 1 and mean AM levels slightly higher than mean PM levels for all treatments on Day 9.

SAFETY RESULTS:

No serious adverse events were reported. The incidence of all adverse events ranged from 29% with EC E20 + naproxen to 50% with PN 400/E30 and PN 400/E20. GI events occurred in 29-32% of subjects with PN 400 treatments and 18% of subjects with EC E20 + naproxen treatment. Iron deficiency, due to frequent blood sampling, was reported as an adverse event in 11% of subjects while on PN 400/E30, 18% with PN 400/E20, and 4% each with PN 400/E10 and EC E20 + naproxen. Most of the adverse events were mild, and no subjects withdrew from the study due to adverse events.

Most laboratory abnormalities were small deviations from the normal range; however, there was a notable decrease in hematocrit, hemoglobin, and/or red blood cell counts at the end of each treatment period for all subjects, likely reflective of frequent blood sampling. Vital sign measurements and physical examination findings were similar at Screening and the Final Visit.

CONCLUSIONS:

- PN 400/E30 and PN 400/E20 treatments resulted in a higher percent time intragastric pH > 4.0 compared to EC E20 + naproxen given separately, after 9 days of treatment
- PN 400/E30, PN 400/E20 and EC E20 + naproxen treatments were similar in percent time intragastric pH > 4.0 after 1 day of treatment
- PN 400/E10 had the lowest percent time with intragastric pH > 4.0 and the highest variability in this response on both Days 1 and 9
- Immediate-release esomeprazole was absorbed rapidly from the PN 400 tablets with plasma concentrations measurable at 10 minutes post dose on Day 1. The AM dose following an overnight fast was absorbed faster and to a greater extent than the PM dose;
- After repeat bid PN 400 doses, plasma esomeprazole concentrations increased substantially as compared to those after the first day of dosing. The magnitude of this increased exposure to esomeprazole after repeat doses was dose dependent
- At steady state (Day 9), esomeprazole AUC_{0-10} was higher for PN 400/E20 than for EC E20 + naproxen and $C_{max,am}$ values following the AM dose of PN 400/E20 on Day 9 were twice as high as EC esomeprazole 20 mg
- Steady-state naproxen plasma profiles were comparable among the three PN 400 dosages, indicating that esomeprazole in PN 400 did not affect the PK of naproxen; plasma profiles of naproxen following PN 400 exhibited delayed absorption characteristics, consistent with the formulation design
- The Day 9 PK and PD profiles of esomeprazole and naproxen demonstrated that immediate-release esomeprazole can be combined with delayed-release naproxen in a dosage form that produces an early onset of increased intragastric pH before naproxen is absorbed
- PN 400 and EC E20 + naproxen treatments were generally well tolerated in 9-day bid treatment periods in healthy subjects
- Based on pH control and low inter-subject variability, PN 400/E20 was selected for studies in subjects at risk for NSAID-associated gastric ulcers

4.1.5 PN 400-105:

Relative BA of Naproxen in PN 400 (naproxen 375 mg/esomeprazole 20 mg)

TITLE: An Open-label, Randomized, Single-Center, Two-Way Crossover Study to Evaluate the Relative Bioavailability of Naproxen Following a Single Oral Dose of PN 400 (375 mg Naproxen/20 mg Esomeprazole) Versus EC-NAPROSYN® 375 mg in Healthy Subjects.

STUDY SITE:

Clinical Site: Pharmaceutical Product Development (PPD)
7551 Metro Center Dr., Suite 200, Austin, TX 78744

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1

OBJECTIVE:

1) To evaluate and compared the pharmacokinetic and relative bioavailability of naproxen from a single oral dose of PN 400 (naproxen 375 mg/ esomeprazole 20 mg) to a single oral dose of EC-ECNAPROSYN® 375 mg, and to determine if PN 400 (375 mg naproxen/20 mg esomeprazole) is bioequivalent to EC-ECNAPROSYN® 375 mg in reference to naproxen component.

2) To evaluate the pharmacokinetic profile of esomeprazole following a single oral dose of PN 400 (naproxen 375 mg/ esomeprazole 20 mg).

3) To evaluate the safety of two treatments.

STUDY DESIGN:

This study was a randomized, open-label, single-center, two-way cross-over study with 30 healthy volunteers (15 males and 15 females). Subjects were randomly assigned to sequences in which they either received a single oral dose of PN 400 table (delayed-released naproxen 375 mg/ immediate-release esomeprazole 20 mg) (treatment A) or EC-ECNAPROSYN® 375 mg (treatment B) in each treatment period following an overnight fast of at least 10 hours. Each treatment dose was administered with 240 mL of water. Each treatment period was 4 days and blood samples were collected up to 72-hours after the initial dose. There was at least 10-days washout interval between two treatment periods.

Subjects were randomized to 1 of following 2 sequences:

Sequence	Number of Subjects	Treatment Period 1	Treatment Period 2
I	15	Treatment A	Treatment B
II	15	Treatment B	Treatment A

Key inclusion criteria:

Healthy males and non-pregnant, non-lactating females ages between 18-55 with Body Mass Index in the range of 18-32 kg/m^2 with negative findings for hepatitis B and C and HIV.

Key exclusion criteria:

- Subject with any gastrointestinal (GI) disease, abnormality or gastric surgery that has potential of interfering with gastric emptying, motility and drug absorption were excluded.
- Subjects who ingested prescription or over-the-counter medications, monoamine oxidase, inhibitors PPIs, H2 antagonists, anticholinergics, OTC anti-ulcer medications, gastric acid altering compounds or naproxen-containing products 14 days preceding the first dosing were also excluded.
- Subject with known allergic reaction, hypesensitivity or intolerance to NSAIDs, esomeprazole or other PPI were also excluded.

Study Population:

This study had 30 healthy volunteers (15 males and 15 females) and all of them completed the study as planned.

Study population demographics:

	Total N=30
Age (years)	
Mean (SD)	33.7 (10.5)
Median	31.0
Range	19-54
Gender, n (%)	
Male	15 (50)
Female	15 (50)
Race, n (%)	
White	26 (87)
Black/African American	3 (10)
Asian	1 (3)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	9 (30)
Not Hispanic or Latino	21 (70)
Height (cm)	
Mean (SD)	169.67 (8.04)
Median	169.00
Range	153.0-187.0
Weight (kg)	
Mean (SD)	74.34 (14.13)
Median	73.75
Range	51.9-99.6

Pharmacokinetic Measurements:
Blood samples were collected at pre-dose, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the administration of oral dose for both treatment groups.

RESULTS:

Pharmacokinetic parameters of naproxen and esomeprazole were determined by non-compartmental method from the plasma concentration vs. time profiles.

SAFETY:

According to the sponsor, all of 30 enrolled volunteers who received single doses of both study drugs completed the study as planned. The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory values, pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse event assessments. 5 subjects in PN 400 375 mg and 2 subjects in EC-ECNAPROSYN® 375 mg had adverse event. All of the reported adverse events were mild. There was no withdrawal due to an adverse event in this study.

Table 4: Overview of Adverse Events – Safety Population

	PN 400 375 mg N=30	**EC NAPROSYN® 375 mg N=30**
	n (%)	n (%)
Subjects with at least 1 adverse event	5 (17)	2 (7)
Subjects with at least 1 treatment-related adverse event	1 (3)	1 (3)
Subjects with at least 1 serious adverse event	0	0
Withdrawals due to adverse events	0	0

Table 5: Summary of Treatment-Emergent Adverse Events – Safety Population

Body System Adverse Event	**PN 400 375 mg N=30**	**EC NAPROSYN® 375 mg N=30**
	n (%)	n (%)
Subjects with at least 1 adverse event	5 (17)	2 (7)
Gastrointestinal disorders	2 (7)	1 (3)
Dyspepsia	0	1 (3)
Flatulence	1 (3)	0
Gingival pain	1 (3)	0
Nervous system disorders	1 (3)	1 (3)
Dizziness	1 (3)	1 (3)
Investigations	1 (3)	0
Bleeding time prolonged	1 (3)	0
Skin and subcutaneous tissue disorders	1 (3)	0
Dermatitis contact	1 (3)	0

SPONSOR'S COMMENTS:

The sponsor concluded that PN 400 375 mg is bioequivalent to EC-NAPROSYN® 375 mg in terms of naproxen pharmacokinetics.

REVIEWER COMMENTS:

- The 90% CI for C_{max} and AUC of naproxen are well within the range of 0.8-1.25. Therefore, the results indicate that the naproxen component of PN400 (delayed-released naproxen 375 mg/ immediate-release esomeprazole 20 mg) is bioequivalent to ECNAPROSYN® 375 mg based on the 90% CI of bioequivalence (BE) acceptance criteria of 80%-125%.

- Following the single dose oral administration of PN 400 table (delayed-released naproxen 375 mg/ immediate-release esomeprazole 20 mg), as suggested by intended immediate-release formulation, esomeprazole was rapidly absorbed (t_{max} = 0.52 hr) followed by a rapid elimination ($t_{1/2}$ = 1.04 hr). Moreover, esomeprazole PK parameters had high inter-subject variability.

- Both drugs (PN400 375 mg and ECNAPROSYN ® 375 mg) are well tolerated when administered as a single dose.

4.1.6 PN 400-106: Relative BA of Celecoxib and Over-Encapsulated Celecoxib

TITLE: A Phase I, single-center, randomized, open-label, two-way crossover study to evaluate the relative bioavailability of a single oral dose of celecoxib administered as a marketed product, or over-encapsulated celecoxib capsule in healthy volunteers

SPONSOR: AstraZeneca Pharmaceuticals

STUDY SITE:

Clinical Site: Bio-Kinetic Clinical Applications, LLC,
1816 West Mount Vernon
Springfield, MO 65802

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

The aim of this study was to evaluate and compare the pharmacokinetics (PK) and bioavailability (BA) of a single oral dose of over-encapsulated celecoxib 200 mg relative to the marketed capsule formulation of celecoxib (200 mg) (Celebrex®) under fasted conditions

STUDY DESIGN:

This study was a randomized, open-label, single-center, single-dose, 2-way cross-over study in 90 healthy volunteers to evaluate the BA of over-encapsulated celecoxib relative to the marketed celecoxib product. Subjects were randomly assigned to one of two treatment sequence as indicated in Tablet 1. Following an overnight fasting of at least 10 hours, each subject received single oral dose of celecoxib (200 mg) as either marketed product (Celebrex®) or over-encapsulated celecoxib with 240 mL water during each treatment period. No food was allowed for at least 4 additional hours after the dose administration. Standardized meals were provided at appropriate times during the study. Water was allowed as desired except 2 hour before and after drug administration. Subjects were not allowed to used antacid day before (24 hr) and day of the study drug dosing (24 hr). For each treatment period, blood samples were collected up to 48 hours after the initial dose. There was at least 7-days washout interval between different treatment periods.

Table 1 Crossover Design

Sequence	Period 1	Period 2	No. of healthy volunteers[a]
1	Celecoxib (Treatment A)	Overencapsulated celecoxib (Treatment B)	40
2	Overencapsulated celecoxib (Treatment B)	Celecoxib (Treatment A)	40

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 18-55 with Body Mass Index in the range of 19-30 kg/m^2 with negative findings for hepatitis B and C and HIV.

Key exclusion criteria:

- Subject with any gastrointestinal (GI) disease, abnormality or gastric surgery that has potential of interfering with gastric emptying, motility and drug absorption were excluded.
- Subjects who ingested prescription or over-the-counter medications, monoamine oxidase inhibitors, PPIs, H2 antagonists, anticholinergics, OTC anti-ulcer medications, gastric acid altering compounds or celecoxib 14 days preceding the first dosing were also excluded.
- Subject with known allergic reaction, hypersensitivity or intolerance to NSAIDs and sulphonamides

Study Population:
This study had 90 healthy volunteers enrolled and 87 of them completed the study as planned, receiving both treatments. Three subjects discontinued study voluntarily. All 90 subjects were included in safety evaluation, and 87 subjects who completed the study were included in PK evaluation.

Table 2: Demographics and Baseline Characteristics

Variable/ Category		Statistic	All subjects N=90
Sex	Male		52 (57.8%)
	Female		38 (42.2%)
Race	White		84 (93.3%)
	Black or African American		4 (4.4%)
	Native Hawaiian or Other Pacific Islander		1 (1.1%)
	Other		1 (1.1%)
Age (years)		Mean	32.7
		SD	11.5
		Minimum	18
		Median	28
		Maximum	55
Height (cm)		Mean	174.4
		SD	8.7
		Minimum	154
		Median	176
		Maximum	188
Weight (kg)		Mean	77.5
		SD	11.6
		Minimum	51
		Median	77
		Maximum	100
BMI (kg/m^2)		Mean	25.5
		SD	3.2
		Minimum	19
		Median	26
		Maximum	30

Pharmacokinetic Measurements:
For each treatment period, blood samples (2 mL each) were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 6, 8, 10, 12, 24, 36, and 48 hours after the administration of oral dose for determination of total celcoxib concentration in plasma.

Pharmacokinetic parameters (Cmax, tmax, AUC0-t, AUC0-inf, t½, , λ_z) of celecoxib were determined by non-compartmental method from the plasma concentration vs. time profiles with WinNonlin Professional software.

Statistical analysis:
Sponsor described their statistical analysis as following:
"The log-transformed PK parameters AUC and Cmax were analyzed using a mixed effects model. Treatment sequence, period and treatment were treated as fixed effects, while subject within sequence was considered as a random effect. From this model, least squares (LS) means and their 95% confidence intervals (CIs) and treatment differences and their 90% CIs were calculated. The results were then transformed back to the original scale by exponentiation to obtain the corresponding geometric LS means with their 95% CI and the geometric means ratios with their 90% CI".

RESULTS:

Intra-subject and Inter-subject Coefficient of Variation for Key Pharmacokinetic Parameters

	Source of Variability	
Pharmacokinetic Parameter (unit)	**Inter-subject %CV**	**Intra-subject %CV**
AUC (h*ng/mL)	34.6	12.1
C_{max} (ng/mL)	36.1	34.0

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory values, and adverse event (AE) assessments. According to the sponsor, there was one serious adverse event, appendicitis, during this study, which was judged to be not related to the investigational product by the investigator. Overall, 26% of healthy volunteers reported to have AE during study and all reported AEs were mild to moderate intensity. The most frequent AEs included headache and nasal congestion. No subjects discontinued due to AEs.

Summary of All Adverse Events by System Organ Class and Preferred Term for Each Treatment

		Number (%) of Subjects		
Severity	**SYSTEM ORGAN CLASS/ Preferred Term**	**Celecoxib N=89**	**Overencapsulated Celecoxib N=89**	**Overall N=90**
Mild	Number of subjects with mild AEs	15 (16.9)	12 (13.5)	23 (25.6)
	GASTROINTESTINAL DISORDERS	4 (4.5)	5 (5.6)	9 (10.0)
	Abdominal pain	1 (1.1)	1 (1.1)	2 (2.2)
	Vomiting	1 (1.1)	1 (1.1)	2 (2.2)
	Constipation	0	1 (1.1)	1 (1.1)
	Diarrhoea	0	1 (1.1)	1 (1.1)
	Dyspepsia	0	1 (1.1)	1 (1.1)
	Flatulence	1 (1.1)	0	1 (1.1)
	Nausea	1 (1.1)	0	1 (1.1)
	Toothache	0	1 (1.1)	1 (1.1)
	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (3.4)	2 (2.2)	4 (4.4)
	Arthralgia	1 (1.1)	1 (1.1)	2 (2.2)
	Back pain	1 (1.1)	0	1 (1.1)
	Pain in extremity	1 (1.1)	1 (1.1)	1 (1.1)

	NERVOUS SYSTEM DISORDERS	8 (9.0)	2 (2.2)	10 (11.1)
	Headache	8 (9.0)	2 (2.2)	10 (11.1)
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (4.5)	4 (4.5)	6 (6.7)
	Nasal congestion	2 (2.2)	4 (4.5)	4 (4.4)
	Cough	1 (1.1)	0	1 (1.1)
	Pharyngolaryngeal pain	1 (1.1)	0	1 (1.1)
Moderate	Number of subjects with moderate AEs	2 (2.2)	1 (1.1)	3 (3.3)
	INFECTIONS AND INFESTATIONS	1 (1.1)	0	1 (1.1)
	Appendicitis	1 (1.1)	0	1 (1.1)
	PSYCHIATRIC DISORDERS	1 (1.1)	0	1 (1.1)
	Agitation	1 (1.1)	0	1 (1.1)
	RENAL AND URINARY DISORDERS	0	1 (1.1)	1 (1.1)
	Dysuria	0	1 (1.1)	1 (1.1)

Summary of Treatment Related Adverse Events by System Organ Class and Preferred Term and Severity for Each Treatment

		Number (%) of Subjects		
Severity	**SYSTEM ORGAN CLASS/ Preferred Term**	**Celecoxib N=89**	**Overencapsulated Celecoxib N=89**	**Overall N=90**
Mild	Number of subjects with mild AEs	9 (10.1)	5 (5.6)	14 (15.6)
	GASTROINTESTINAL DISORDERS	2 (2.2)	3 (3.4)	5 (5.6)
	Abdominal pain	0	1 (1.1)	1 (1.1)
	Constipation	0	1 (1.1)	1 (1.1)
	Diarrhoea	0	1 (1.1)	1 (1.1)
	Dyspepsia	0	1 (1.1)	1 (1.1)
	Flatulence	1 (1.1)	0	1 (1.1)
	Nausea	1 (1.1)	0	1 (1.1)
	NERVOUS SYSTEM DISORDERS	8 (9.0)	2 (2.2)	10 (11.1)
	Headache	8 (9.0)	2 (2.2)	10 (11.1)

REVIEWER'S COMMENTS:

The over-encapsulated celecoxib formulation is bioequivalent to the marketed formulation of celecoxib capsule under fasted conditions.

4.1.7 PN 400-111: Intra-Subject Variability of Esomeprazole PK

TITLE: An Open-label, 2-Period Pharmacokinetics Study to Evaluate the Intra-Subject Variability in Esomeprazole Plasma Levels in Healthy Subjects Following Oral Administration of PN 400 Tablets

STUDY SITE:

Clinical Site: Pharmaceutical Product Development (PPD)
7551 Metro Center Dr., Suite 200, Austin, TX 78744

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

1. To determine the intra-subject variability in plasma esomeprazole levels in healthy subjects following a single dose and repeat twice-daily (BID) doses of PN 400 tablets from the same drug product batch
2. To evaluate the safety of PN 400 in each of treatment periods.

STUDY DESIGN:

This study was an open-label, single-center, 2 treatment period study with 18 healthy volunteers to assess the intra-subject variability of esomeprazole plasma levels following a single s and multiple doses. In each treatment period, each subject received oral dose of PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg) once a day on Day 1 and Day 10 in the morning (AM dose) and twice a day on Days 2-9 (AM and PM doses) with 240 mL of water. Each AM dose on Day 1-10 were administered following an over night fasting (as of midnight) followed by a breakfast approximately 1 hr later. The PM doses on Days 2-9 were administered in the clinic approximately 10 hr after the AM dose followed by a meal approximately 1 hr later, and food was not allowed for 2 hr prior to the PM dose. On Day 1 and 10, blood samples were collected up to 24 hr after the AM doses, and subjects received standardized meal and beverages on these two days. Each subjects received the same treatment over two separate periods and the treatment procedure in second treatment period was same as the first treatment period. Two treatment periods were separated by 13-days of washout interval.

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 18-55 with Body Mass Index in the range of 19-32 kg/m^2 with negative findings for *H. pylori*.

Key exclusion criteria:

- Subject with any gastrointestinal (GI) disease, or surgery that has potential of interfering with drug absorption were excluded.
- Subject with known allergic reaction, hypersensitivity or intolerance to NSAIDs, esomeprazole or other PPI or a significant history of peptic ulcer disease or other acid-related gastrointestinal symptoms were also excluded.

Study Population:
This study had 18 healthy volunteers (7 males and 11 females) enrolled and 17 of them completed the study as planned, receiving both treatments. One subject withdrew due to course of antibiotic therapy begun during the washout period due to development of bronchitis during the 1st treatment period.

Table1: Summary of demographics and Baseline Characteristics Safety Population

	PN 400 N=18
Age (years)	
Mean (SD)	32.1 (11.2)
Median	27.5
Range	22-52
Gender – n (%)	
Male	7 (39)
Female	11 (61)
Race – n (%)	
White	12 (67)
Black/African American	6 (33)
Other	0
Ethnicity – n (%)	
Hispanic or Latino	6 (33)
Not Hispanic or Latino	12 (67)
Height (cm)	
Mean (SD)	166.7 (9.4)
Range	150.5 – 185.5
Weight (kg)	
Mean (SD)	74.9 (13.6)
Range	53.1 – 102.8

Pharmacokinetic Measurements:
On day 1 and 10, plasma samples were collected at pre-dose, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the administration of AM dose for each treatment period.

Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24}, AUC_{0-inf}, $t_{½}$) of esomeprazole were determined from the plasma concentration vs. time profiles from Day 1 (single dose) and Day 10 (repeat dose) for each treatment period by non-compartmental method with WinNonlin Professional software.
Inter-subject (between-subject) variability, %CVb (expressed as % coefficient of variation), was calculated using natural log-transformed values for C_{max}, AUC, and t1/2 according to the following formula:

$$\%CVb = \sqrt{\exp((SD\ of\ \ln-transformed)^2)-1}\ \text{x}\ 100$$

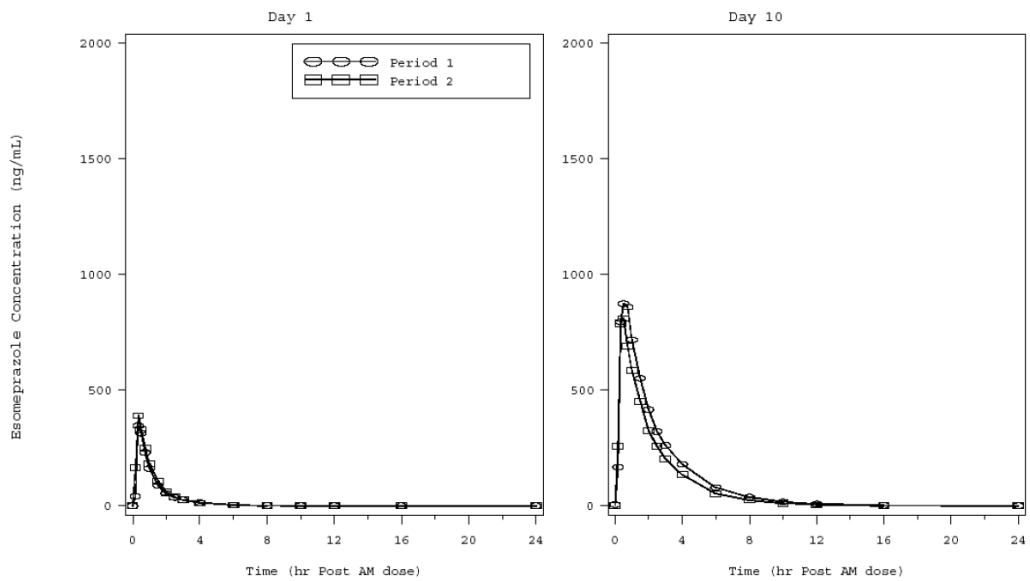
Analysis of variance (ANOVA) was performed on the logarithmic (log)-transformed PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} to evaluate the intra-subject variability of esomeprazole from PN 400 after a single dose (day 1) and repeat BID does (day 10). The ANOVA model included period and subject as fixed effects. The geometric least-squares mean (LSM) ratio between periods and associated 90% CIs for AUCs and C_{max} were determined. The intra-subject variability (within-subject coefficient of variation (CVw)) was calculated based on the log -normal distribution:

$$\text{CVw (\%)} = \sqrt{\exp(MSE) - 1} \text{ x } 100$$

where MSE was the mean square error obtained from the ANOVA.

RESULTS:

Figure 1. Mean Plasma Esomeprazole Concentration vs. Time Curves



- On day 1, esomeprazole concentration was measurable up to 6-8 hr post dose in each period.
- On day 10, esomeprazole concentration was measurable up to 10-12 hr post dose in each period.
- The pre-AM-dose samples on Day 10 had measurable esomeprazole concentrations in approximately 50% of the subjects in both periods.
- Plasma concentrations vs. time profiles are almost superimposable between two treatments in both day 1 and day 10.

Table 2: Summary of Esomeprazole Pharmacokinetic Parameters by Period and Study Day

Period	Day	Statis-tics	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	t½ (hr)	AUC_{0-inf} (hr*ng/mL)
1	1	Mean	383		383	385	0.99	385
		%CV	87		98	97	27	97
	n = 17	Median	262	0.33	241	243	0.93	243
		Min	55.4	0.33	78.0	81.4	0.62	81.4
		Max	1130	1.00	1586	1588	1.53	1588
		Geom Mean	271		267	270	0.95	270
		%CVb	107		105	104	28	104
1	10	Mean	1080		2215	2219	1.53	
		%CV	53		74	74	43	
	n = 17	Median	1200	0.50	2003	2005	1.37	
		Min	171	0.33	138	145	0.68	
		Max	1890	0.77	5668	5668	2.91	
		Geom Mean	859		1414	1423	1.40	
		%CVb	96		168	166	44	
2	1	Mean	451		433	436	0.95	436
		%CV	80		72	72	23	72
	n = 17	Median	314	0.50	489	493	0.85	493
		Min	52.2	0.17	51.4	53.4	0.71	53.4
		Max	1130	0.75	1031	1033	1.53	1033
		Geom Mean	297		308	313	0.93	313
		%CVb	138		120	117	22	117
2	10	Mean	954		1772	1776	1.31	
		%CV	47		64	64	34	
	n = 17	Median	871	0.33	1977	1985	1.27	
		Min	162	0.17	194	198	0.71	
		Max	1630	1.00	3776	3787	2.36	
		Geom Mean	825		1314	1320	1.24	
		%CVb	69		114	114	35	

- On day 10, following multiple BID doses of PN 400, esomeprazole concentration was much higher compared to day 1 in both periods (2.78-317 folds higher in C_{max} and 4.22-5.26 folds higher in AUC).
- Half lives on Day 10 were longer then Day 1 for both treatments.
- Very large inter-subject variability in PK parameters, 69%-138% for C_{max} and 104%-168% for AUC values

Table 3: Statistical Analysis of Esomeprazole C_{max} and AUC Values between Treatment Periods within Individuals on Days 1 and 10

PK Parameter	Day	Geom LS Mean Period One	Geom LS Mean Period Two	MSE (%)	%CVw
Cmax	1	271.0	297.0	56.84	61.76
	10	858.5	824.5	45.40	47.84
AUC_{0-24}	1	270.3	312.5	47.44	50.24
	10	1423.0	1320.0	62.49	69.11

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory values (hematology, chemistry, urinalysis), 12-lead electrocardiogram (ECG), and adverse event (AE) assessments. During the study, 13 subjects experienced AE, none being serious, and only one subject had treatment-related AE. According to the sponsor, all of the reported adverse events were mild.

Table 4: Overview of Adverse Events-Safety Population

	PN 400 N=18
	n (%)
Subjects with at least one adverse event	13 (72)
Subjects with at least one drug-related adverse event	1 (6)
Subjects with at least one serious adverse event	0
Deaths	0
Withdrawals due to adverse events[1]	0

Table 5: Summary of Treatment-Emergent Adverse Events-Safety Population

System Organ Class Preferred Term	PN 400 N=18
	n (%)
Subjects with any adverse event	13 (72)
Infections and infestations	6 (33)
Viral infection	4 (22)
Bronchitis	1 (6)
Nasopharyngitis	1 (6)
Respiratory, thoracic and mediastinal disorders	5 (28)
Pharyngolaryngeal pain	2 (11)
Cough	1 (6)
Epistaxis	1 (6)
Nasal congestion	1 (6)
Gastrointestinal disorders	3 (17)
Abdominal pain	1 (6)
Dry mouth	1 (6)
Nausea	1 (6)
General disorders and administration site conditions	2 (11)
Asthenia	1 (6)
Feeling hot	1 (6)
Hunger	1 (6)
Nervous system disorders	2 (11)
Insomnia	1 (6)
Somnolence	1 (6)
Musculoskeletal and connective tissue disorders	1 (6)
Back pain	1 (6)
Skin and subcutaneous tissue disorders	1 (6)
Rash maculo-papular	1 (6)

REVIEWER'S COMMENTS:

Both single and multiple doses (steady state) of PN 400 resulted in a very large inter- and intra-subject variability in the esomeprazole PK parameters:

- Inter-subject variability (CVb) across study days and periods:
  - 69%-138% for Cmax

    - 104%-168% for AUC
- Intra-subject variability (CVw):
    - 62% on Day 1 and 48% on Day 10 for C_{max}
    - 50% on Day 1 and 69% on Day 10 for AUC_{0-24}

Although large intra- and inter-subject variability of esomeprazole PK was thought to be partially due to the immediate-release nature of the formulation, introducing esomeprazole to a variable amount of gastric acid degradation, reaching steady state in gastric acid inhibition with repeated administration of esomeprazole did not reduce esomeprazole's inter and intra-individual variability.

4.1.8 PN 400-114: BA of Esomeprazole and BE of Naproxen

TITLE: A Randomized, Open-Label, 4-Way Crossover Study to Evaluate Naproxen and Esomeprazole Plasma Levels in Healthy Subjects Following Oral Administration of PN 400, Enteric-Coated Naproxen 500 mg Plus Enteric-Coated Esomeprazole 20 mg, Enteric-Coated Naproxen 500 mg Alone, and Enteric-Coated Esomeprazole 20 mg Alone

STUDY SITE:

Clinical Site: Pharmaceutical Product Development (PPD)
7551 Metro Center Dr., Suite 200, Austin, TX 78744

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

1. To assess the single-dose pharmacokinetics and relative bioavailability of esomeprazole in PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg), the enteric-coated (EC) naproxen 500 mg plus EC esomeprazole 20 mg, and the EC esomeprazole 20 mg alone treatments.

2. To assess the single-dose pharmacokinetics, relative bioavailability and bioequivalence of naproxen in the PN 400 (delayed-release naproxen 500 mg /immediate-release esomeprazole 20 mg), the EC naproxen 500 mg plus enteric-coated esomeprazole 20 mg, and the EC naproxen 500 mg alone treatments.

3. To evaluate the safety of each of the single-dose treatments

STUDY DESIGN:

This study was a randomized, open-label, single-center, 4-way cross-over study with 40 healthy volunteers (approximately 20 males and 20 females) to evaluate the PK and relative BA of esomeprazole and naproxen from PN 400 (delayed-release naproxen 500 mg / immediate-release esomeprazole 20 mg). Subjects were randomly assigned to one of the 4 treatment sequences indicated in Table-1. Following an overnight fasting of at least 10 hours, each subject received single dose of each of following 4 treatments (Table 2) in cross over study design based on the randomization schedule with 240 mL of water. No food was allowed for at least 4 additional hours after the dose administration. Standardized meals were provided at appropriate times during the study. Water was allowed as desired except 1 hour before and1 hour after drug administration. For each treatment blood samples were collected up to 72-hours, except for treatment D (blood collection up to 12hr) after the initial dose. There was at least 12-days washout interval between different treatment periods.

Table-1

Sequence	Number of Subjects	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
I	10	A	D	B	C
II	10	B	A	C	D
III	10	C	B	D	A
IV	10	D	C	A	B

Table-2

Treatment	Study Medication
A	PN 400 (delayed-release naproxen 500 mg / immediate release esomeprazole 20 mg) tablet
B	EC naproxen 500 mg tablet (EC Naprosyn ®) plus EC esomeprazole 20 mg capsule (Nexium®)
C	EC naproxen 500 mg tablet (EC Naprosyn ®) (Roche Pharmaceuticals)
D	EC esomeprazole 20 mg capsule (Nexium®) (AstraZeneca)

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 18-55 with Body Mass Index in the range of 18-32 kg/m^2 with negative findings for hepatitis B and C and HIV.

Key exclusion criteria:

- Subject with any gastrointestinal (GI) disease, abnormality or gastric surgery that has potential of interfering with gastric emptying, motility and drug absorption were excluded.
- Subjects who ingested prescription or over-the-counter medications, monoamine oxidase, inhibitors PPIs, H2 antagonists, anticholinergics, OTC anti-ulcer medications, gastric acid altering compounds or naproxen-containing products 14 days preceding the first dosing were also excluded.
- Subject with known allergic reaction, hypersensitivity or intolerance to NSAIDs, esomeprazole or other PPI or a significant history of peptic ulcer disease or other acid-related gastrointestinal symptoms were also excluded.

Study Population:

This study had 40 healthy volunteers (20 males and 20 females) enrolled and 37 of them completed the study as planned, receiving all four treatments. Of 3 discontinued subjects, 2 of them discontinued for personal reasons and 1 subject withdrew consent.

Table 3: Subject Disposition – All Randomized Subjects

	Number of Subjects (%) N=40
Subjects Randomized and Treated	40 (100)
Safety Population	40 (100)
PK Population	40 (100)
Subjects Completed	37 (93)
Subjects Withdrawn Prematurely	3 (8)
Adverse event	0
Withdrew consent	1 (3)
Lost to follow-up	0
Other	2 (5)

Table 4: Demographic Characteristics – Safety Population

	Total Subjects N=40
Age (years), n (%)	
N	40
Mean (SD)	32.9 (9.5)
Median	31.0
Range	18 – 54
Gender, n (%)	
Males	20 (50)
Females	20 (50)
Race, (%)	
White	34 (85)
Black/African American	5 (13)
Asian	1 (3)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	14 (35)
Not Hispanic or Latino	26 (65)
Height (cm)	
N	40
Mean (SD)	168.76 (7.50)
Median	168.50
Range	155.0 – 183.5
Weight (kg)	
N	40
Mean (SD)	73.17 (11.95)
Median	72.40
Range	49.8 – 95.4

Pharmacokinetic Measurements:

For each treatment period, blood samples (3 mL each) were collected at pre-dose, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 36, 48 and 72 hours after the administration of oral dose for each treatment

groups (31 blood samples/period). For administration of EC-esomeprazole alone (treatment D), blood samples were collected up to 12 hr (22 blood samples/period).

Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{½}$, $\%AUC_{extrap}$) of naproxen and esomeprazole in individual subjects were determined by non-compartmental method from the plasma concentration vs. time profiles with WinNonlin Professional software.

Analysis of variance (ANOVA) was performed on the logarithmic (log)-transformed PK parameters AUC_{0-t}, AUC_{0-inf} and C_{max} to evaluate the relative bioavailability of esomeprazole and naproxen between treatments. The ANOVA model included sequence, period and treatment as fixed effects, and subject within sequence as a random effect. The geometric least-squares means ratios between treatments and the associated 90% confidence intervals for AUCs and C_{max} were calculated.

RESULTS:

Of 40 enrolled healthy subjects, 38 subjects received single doses of Treatment A and 39 subjects received single doses of Treatment B, C and D.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory values, pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse even (AE)t assessments. According to the sponsor, there were no serious adverse events or withdrawals due to adverse events. 3% within treatment C and 15% with Treatment B had adverse events. The most frequent AEs included dizziness, headache, and nausea or pharyngolaryngeal pain. All of the reported adverse events were mild.

Table 10: Overview of Adverse Events – Safety Population

Treatment	A PN 400 N = 38	B EC Nap + EC Eso N = 39	C EC Nap N = 39	D EC Eso N = 39
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 adverse event	3 (8)	6 (15)	1 (3)	2 (5)
Subjects with at least 1 serious adverse vent	0	0	0	0
Deaths	0	0	0	0
Withdrawals due to adverse events	0	0	0	0

Table 11: Treatment-Emergent Adverse Events – Safety Population

System Organ Class Adverse Event	A PN 400 N=38	B EC Nap + EC Eso N=39	C EC Nap N=39	D EC Eso N=39
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 adverse event	3 (8)	6 (15)	1 (3)	2 (5)
Nervous system disorders	2 (5)	3 (8)	0	2 (5)
Dizziness	1 (3)	2 (5)	0	1 (3)
Headache	0	2 (5)	0	1 (3)
Syncope	1 (3)	0	0	0
General disorders and administration site conditions	1 (3)	1 (3)	1 (3)	0
Chest discomfort	0	0	1 (3)	0
Cyst	1 (3)	0	0	0
Pain	0	1 (3)	0	0
Pyrexia	0	1 (3)	0	0
Respiratory, thoracic and mediastinal disorders	0	3 (8)	0	0
Pharyngolaryngeal pain	0	3 (8)	0	0
Cough	0	1 (3)	0	0
Gastrointestinal disorders	0	1 (3)	0	0
Nausea	0	1 (3)	0	0
Injury, poisoning and procedural complications	1 (3)	0	0	0
Head Injury	1 (3)	0	0	0

COMMENTS:

- For BE study of each component of PN 400, since there is no immediate-release (IR) esomeprazole marketed product available, a commercially available enteric coated esomeprazole product (EC Nexium®) was used instead.

- The 90% CI for C_{max} and AUC of naproxen are well within the acceptable range of 0.8-1.25. Therefore, PN400 (delayed-released naproxen 500 mg/ immediate-release esomeprazole 20 mg) is bioequivalent to ECNAPROSYN ® 500 mg in terms of Naproxen C_{max} and AUC.

- The extent of esomeprazole bioavailability from single dose of IR formulation (PN 400) is about 50% that of EC formulation (EC Nexium®) in presence and absence of naproxen.

- Co-administration of naproxen and esomeprazole do not affect each other PK profile regardless of esomeprazole formulation (IR or EC) indicating absence of pharmacokinetic interaction between the two components of PN 400.

    - Naproxen PK was not altered with co-administration of IR or EC esomeprazole.

- Extent of EC esomeprazole bioavailability did not change with co-administration of EC naproxen.

- Half life of esomeprazole in PN 400 with 500 mg naproxen is consistent that of PN 400 with 375 mg naproxen.
-
- Half life of naproxen from PN 400 and NAPROSYN ® did not change with dose (375 mg or 500 mg) (comparison with study PN 400-105)

- All Studies were well tolerated

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4.1.10 Articles:

Segre EJ, Chaplin M, Forchielli E, Runkel R, Sevelius H; Naproxenaspirin interactions in man. Clin Pharmacol and Ther 15(4), 374-379.

Naproxen-aspirin interactions in man

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4.2 Cover sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**NDA 22-511**	**Brand Name**	**Vimovo®**
OCP Division (I, II, III)	**III**	**Generic Name**	**Esomeprazole/naproxen**
Medical Division	**Gastroenterology**	**Drug Class**	**Proton pump inhibitor/NSAID**
OCP Reviewers	**PeiFan Bai**	**Indication(s)**	**Signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID associated gastric ulcers**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Tablets**
Date of Submission	**June 30, 2009**	**Proposed Dosing Regimen**	**Naproxen 375 mg or 500 mg/esomeprazole 20 mg**
Estimated Due Date of OCP Review	**Feb 30, 2010**	**Route of Administration**	**oral**
Medical Division Due Date		**Sponsor**	**Pozen**
PDUFA Due Date	**April 30, 20010**	**Priority Classification**	**Standard**

Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**	**10**		
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**10**		
1.1 Healthy Volunteers-				
single dose:	**X**	**6**		**PK/PD**
multiple dose:	**X**	**4**		**1 study: PK; 2 studies: PK/PD; 1 study: food effect**
1.1.1 Patients-				
single dose:				
multiple dose:	**X**	**4**		**Safety & efficacy**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**		**350 mg & 500 mg naproxen; 500 mg naproxen & Esomeprazole: 10mg, 20 mg, 30 mg**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	**X**	**1**		**Study 104: Healthy (intragastric pH), 500 mg naproxen & Esomeprazole: 10mg, 20 mg, 30 mg**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		**Combination product vs individual component**
Bioequivalence studies -				
traditional design; single / multi dose:	**single**	**3**		**Studies 102 & 105: BE with regard to naproxen (350 mg & 500 mg)**
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		**Food effect**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies	**10**	**10**		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm	**x**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **What are the design features of the submitted studies used to support the labeling claims and fulfillment of PWR?**	
Other comments or information not included above		

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DILARA JAPPAR
04/07/2010

SUE CHIH H LEE
04/07/2010

PEIFAN J BAI
04/08/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-511 (N-000)
Submission Date:	06/30/09 and teleconferences (10/20/09 and 02/24/10)
Brand Name:	Vimovo
Generic Name:	Naproxen/Esomeprazole
Formulation:	Naproxen Delayed release (DR)/Esomeprazole (Eso) magnesium immediate release (IR) fixed dose combination (FDC) tablets
Strength:	500/20 mg and 375/20 mg
Sponsor:	Pozen
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

EXECUTIVE SUMMARY

Naproxen is an approved non-steroid anti-inflammatory drug (NSAID) and DR-Naprosyn (naproxen) 375 and 500 mg oral tablets are currently on the market. Eso is a proton pump inhibitor (PPI) to suppress gastric acid secretion. Nexium (Eso magnesium) 20 and 40 mg enteric coated (i.e., delayed release) pellets in caps are approved by the Agency.

On 06/30/09, Pozen submitted NDA 22-511 (N-000) for Vimovo FDC tablet. It is a single combination tablet of two distinct formulations, an inner enteric coated core tablet of naproxen containing either 375 mg or 500 mg of naproxen and an outer IR film coating including 20 mg of Eso. Vimovo is intended for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers and their complications.

Vimovo 500/20 mg FDC tablet batches (including several primary stability batches) were tested in Phase 1 clinical pharmacology studies and also in the clinical Phase 3 pivotal studies. Although Vimovo 375/20 mg FDC tablet batches had never been tested in Phase 3 clinical trials, a primary stability batch of 375/20 mg tablet was tested in a Phase 1 clinical pharmacology study. This NDA was accepted for filing and no biowaiver request was needed.

Dissolution testing using various media, USP apparatus and agitation speeds were carried out and dissolution methodology and specifications for Vimovo FDC tablets were selected for approval and submitted for review.

Several meetings were held internally with ONDQA as well as two teleconferences (Telecon) with the sponsor regarding their proposed dissolution methodology. It was concluded that from the Biopharmaceutics perspective, there is no approvability issue, however, the sponsor's proposed dissolution methodology was not optimal. Please see the following Comment section, Comment No. 1 for details.

In the Telecon with the sponsor on 02/24/10, the sponsor agreed that their proposed dissolution methodology and specifications could be used on an interim basis if the NDA

is approved. Please see the following Comment No. 2 for details. The sponsor also agreed that as a Phase 4 commitment, 1). the USP dissolution methodology should be used for testing naproxen of the Vimovo FDC tablets and 2) within one year post-approval, the sponsor should submit new dissolution data for review. Please see the following Comment No.3 below.

COMMENTS (Need to be sent to the sponsor)

1. (b) (4)

   The above proposed dissolution methodology for naproxen is considered not optimal. The reasons are as follows:

   a. (b) (4)

   b. The conventional USP dissolution methodology mimics and therefore, is closer to the physiological conditions in the stomach when the tablet is first administered.

2. As agreed upon in the 02/24/10 Telecon, your proposed methodology and specifications can be used on an interim basis as shown below.

   I. Acid Stage: for naproxen only
   USP Apparatus 2 (with sinkers) at 75 rpm
   Medium: 475 mL of 0.1 M HCl at 37°C
   Time: 2 hours
   Q= not more than (NMT) (b) (4)

   II. Buffer Stage: for both esomeprazole and naproxen (using a second set of tablets).
   USP Apparatus 2 (with sinkers) at 75 rpm
   Medium: 900 mL of 0.05 M phosphate buffer pH 7.4 at 37°C
   Time: 15, 30, 45, 60, and 75 minutes
   Q= (b) (4) **in 60 minutes for naproxen**
   Q= (b) (4) **in 60 minutes for esomeprazole**

However, the specifications for esomeprazole need to be tightened as follows:

From the proposed **Q=** (b) (4) **in 60 minutes**
to **Q** (b) (4) **in 45 minutes**.

3. As a Phase 4 commitment, within one year post approval, you need to submit new dissolution data on the testing of naproxen in Vimovo FDC tablets using the Agency's recommended USP dissolution methodology for enteric coated (i.e., delayed release) drug products as shown below.

   I. For Naproxen: (one set of tablets)

   <u>Acid stage</u>:
   USP Apparatus 2 (paddle) at 75 rpm
   Medium: 475 mL of 0.1 M HCl at 37°C
   Time: 2 hours
   Q= (b) (4)

   Followed by

   <u>Buffer stage</u>:
   USP Apparatus 2 (paddle) at 75 rpm
   Medium: 900 mL of 0.05 M phosphate buffer pH 7.4 at 37°C

   The specifications for naproxen in the buffer stage will be revisited once the data is generalized and reviewed by the Agency.

   II. For Esomeprazole: (another set of tablets)

   Since Esomeprazole is acid labile and not enteric coated, it degrades in the acid stage. Another set of tablets for testing esomeprazole only in the buffer stage (without pre-exposure to acid stage) using your proposed dissolution methodology with a tightened specification (**Q** (b) (4) **in 45 minutes**) is acceptable.

RECOMMENDATION

From the Biopharmaceutics perspective, there is no approvability issue. The dissolution data submitted are acceptable, however, the currently proposed dissolution methodology by the sponsor for Vimovo FDC tablets can only be used on an interim basis. As a Phase 4 commitment, the sponsor agreed to submit additional dissolution testing/data on the naproxen of Vimovo FDC tablets for review. The above Biopharmaceutics comments need to be conveyed to the sponsor.

BACKGROUND

Naproxen is a non-steroid anti-inflammatory analgesic. DR-Naprosyn (naproxen) 375 and 500 mg oral DR tablets under NDA 20-367 was approved on 10/14/94. Eso is a PPI which suppresses gastric acid secretion. Nexium (Eso magnesium) 20 and 40 mg enteric coated pellets in caps under NDA 21-153 was approved on 02/20/01.

CURRENT SUBMISSION

On 06/30/09, Pozen submitted NDA 22-511 (N-000) for Vimovo FDC tablet. It is a single combination tablet of two distinct formulations, an inner enteric coated (i.e., DR) component of naproxen containing either 375 mg or 500 mg of naproxen and an outer immediate release (i.e., IR) film coat containing 20 mg of Eso (present as 22.3 mg of esomeprazole magnesium trihydrate).

Vimovo tablets are intended for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers and their complications.

Dissolution testing using various media, apparatus, and agitation speeds were explored. Individual and mean dissolution data plus mean dissolution profiles of the clinical and primary stability batches using the selected methodology were submitted for review.

FORMULATION COMPARISONS

Vimovo tablet consists of a naproxen core tablet that is coated with six film coats, i.e., a sub film coat, enteric film coat, barrier film coat, Eso film coat, color film coat, and finish film coat. Figure 1 illustrates the construction of the product.

Figure 1 Schematic of PN 400 Tablet (not to scale)

(b) (4)

The composition/formulation of Vimovo 500/20 mg and 375/20 mg FDC tablets are shown below.

Table 1. Composition/Formulation of Vimovo FDC Oral Tablets

Component	Quantity per unit (mg/tablet)			
	Initial Phase 1 500 mg/20 mg	Phase 3 500 mg/20 mg[a]	Primary stability 500 mg/20 mg[b]	Primary stability 375 mg/20 mg[c]
				(b) (4)
Total film coated tablet weight	745	745	745	581

NA Not applicable.
q.s. quantum satis (as much as suffices).
[a] Phase 3 formulation also used in Phase 1 bioequivalence study PN400-102 and Phase 1 PK study PN400-111.
[b] Primary stability formulation is identical to commercial formulation and was used in Phase 1 bioequivalence study PN400-114 and food effect study PN400-103.
[c] Primary stability formulation is identical to commercial formulation and was used in Phase 1 bioequivalence study PN400-105.
[d] Stated as dry weight.
[e] (b) (4)

The sponsor reported that 1) the naproxen core is the same as the currently approved Roche's DR-Naprosyn tablet plus incorporation of a (b) (4) and 2) the to-be-marketed (TBM) formulation of Vimovo is the same as that of the primary stability.

The Vimovo 500/20 mg FDC tablet of a primary stability batch was employed in a Clinical Pharmacology (clinpharm) study No. PN400-114 comparing 1) with the coadministration of the approved DR Naprosyn 500 mg tablet and Nexium 20 mg cap and 2) with the individual components (a 4x4 study). The Vimovo 500/20 mg FDC tablet batch made for Phase III Study No. PN400-302 was also employed in a clinpharm study No. PN400-102 comparing 1) with the approved DR Naprosyn 500 mg tablet and 2) a DR-naproxen core 500 mg tablet (a 3x3 study).

The Vimovo 375/20 mg tablet batches were never used in any Phase 3 clinical trials. However, one primary stability batch of Vimovo 375/20 mg FDC tablet was used in a clinpharm study No. PN400-105 comparing it with the approved DR-Naprosyn 375 mg tablet (a 2x2 study).

The details of the primary stability batches used in the clinical studies are shown in Appendix 1.

DISSOLUTION COMPARISONS

(b) (4)

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(b) (4)

[redacted]

Reviewer's Comments:

1. There are differences in dissolution profiles and implications between the sponsor's proposed methodology and the conventional USP dissolution methodology proposed in the Agency's guidance for delayed release drug products. The dissolution profiles of naproxen with and without pre-exposure of Vimovo FDC tablets in the acid stage are shown below.

(b) (4)

[redacted]

Thus, it is recommended that for the dissolution testing for the naproxen component of the Vimovo FDC tablets, the conventional dissolution methodology for delayed release product, i.e., in the acid stage (pre-exposure) followed by the buffer stage be performed.

2. Since Eso is acid labile and not enteric coated, it degrades in the acid stage. Another set of tablets for testing Eso in the buffer stage (without pre-exposure to acid stage) is acceptable, however, the specification for Eso should be tightened.

_____ ___02//05/10, 03/02/10_____

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ ___02//05/10, 03/02/10_____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 22-511 for Vimovo (Naproxen DR /Esomeprazole IR) FDC Tablets, 500/20 mg and 375/20 mg

Appendix 1

Details of Batches Used in Clinical Studies

Table . Details of Batches Used in Key Phase 1 Clinical Pharmacology Studies

Study No.	Formulation	Study Purpose	Drug Products	Batch No.
PN400-101 and PN400-104	Phase 1	Proof of concept and Dose finding	PN 400 (500 mg/10 mg) PN 400 (500 mg/20 mg) PN 400 (500 mg/30 mg)	3056996R 3056997R 3056998R
PN400-102	Phase 3	Bioequivalence for 500 mg naproxen	PN 400 (500 mg/20 mg) EC Naproxen (500 mg) EC NAPROSYN® (500 mg)	3059037R[a] 3059032R[b] U4711
PN400-103	Primary stability/ Commercial formulation	Food Effect	PN 400 (500 mg/20 mg)	3064068R
PN400-114	Primary stability/ Commercial formulation	Pharmacokinetic and Bioequivalence	PN 400 (500 mg/20 mg) EC NAPROSYN® (500 mg) NEXIUM®[1] (20 mg)	3064068R[a] E0001E1 U7048
PN400-105	Primary stability/ Commercial formulation	Bioequivalence for 375 mg naproxen	PN 400 (375 mg/20 mg) EC NAPROSYN® (375 mg)	3064071R[a] E0001E1

EC Enteric coated.
[a] Individual values for esomeprazole and naproxen dissolution profiles (n=12) for the PN 400 Tablet batches are provided in Table 20 and Table 21, respectively.
[b] Individual values for naproxen dissolution profiles (n=12) for the EC Naproxen batch are provided in Table 22.

Table . Details of Batches Used in Phase 3 Clinical Studies

Study No.	Formulation	Study Purpose	Drug Products	Batch No.
PN400-301	Phase 3	Pivotal efficacy	PN 400 (500 mg/20 mg)	3059034R 3059037R
			EC Naproxen (500 mg)	3059032R 3060740R
PN400-302	Phase 3	Pivotal efficacy	PN 400 (500 mg/20 mg)	3059035R 3059038R
			EC Naproxen (500 mg)	3059032R 3060740R
PN400-304	Phase 3	Long term safety	PN 400 (500 mg/20 mg)	3059034R 3059035R 3059036R 3059217R

EC Enteric coated.

NDA 22-511 for Vimovo (Naproxen DR /Esomeprazole IR) FDC Tablets, 500/20 mg and 375/20 mg

Appendix 2

Individual and Mean Dissolution Data of Tested Batches Using the Proposed Dissolution Methodology

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
03/08/2010

PATRICK J MARROUM
03/09/2010