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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Naproxen/Esomeprazole
Magnesium
Trade Name Vimovo
Therapeutic Class Combination NSAID and Proton
Pump Inhibitor
Applicant Pozen Inc
Formulation(s) Oral tablet
Dosing Regimen Naproxen (500 or 375mg) and
Esomeprazole (20mg) twice daily
Indication(s) Treatment of signs and symptoms
of osteoarthritis, rheumatoid
arthritis, and ankylosing
spondylitis in participants are risk
for developing NSAID-associated
gastric ulcers.
Intended Population(s) Adults 18 years and above

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The sponsor has proposed the following indication for Vimovo tablets: relief of signs and symptoms of osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis in patients at risk of developing NSAID-associated gastric ulcers.

In reference to the reduction of gastric ulcers, based on the data provided, this medical reviewer recommends approval for the aforementioned indication. The sponsor has provided evidence that Vimovo was superior to the active control (EC Naproxen) in decreasing the incidence of NSAID-induced ulcer formation. The proportion of patients developing gastric ulcers while taking Vimovo was statistically lower than the proportion of patients taking EC Naproxen (5.6% vs. 23.7%). It is important to note that in the opinion of this medical officer, it has been well documented that all patients taking NSAIDs chronically are at risk of ulcer formation. In this medical officer's opinion, the sponsor has not studied patients at high-risk of developing complications from NSAID-induced GI toxicity. The one clinical trial (PN400-303) designed to support this claim was terminated early.

Review of this NDA was done with consultation from the Division of Anesthesiology and Rheumatology Products. Per the DAARP consult, superiority of Vimovo to placebo was established for the indication of the treatment of the signs and symptoms of osteoarthritis based on primary ITT/LOCF analysis and three sensitivity analyses. Together, the bioequivalence of the naproxen in Vimovo tablets to the reference drug (EC Naproxen) and the superiority of Vimovo to placebo for pain reduction provide adequate evidence of efficacy for the proposed indication from DAARPs perspective.

1.2 Risk Benefit Assessment

The current submission is a 505(b)(2) application using Nexium® and EC Naprosyn® as the reference listed drugs. The enteric coated naproxen component of Vimovo has been shown to be bioequivalent with EC Naprosyn®. The nexium component is immediate release and initially has half of the bioavailability of the equivalent dose of Nexium®. However, cumulative dosing of Vimovo increases the bioavailability of the Nexium® component.

Both of the reference listed drugs have been marketed in the United States for a number of years and have been used concurrently in patients at risk of developing ulcers due to chronic NSAID use. Given the information that has been provided in the sponsor's application, Vimovo was effective for pain reduction and reduction in ulcer

formation. Based on the information provided, it is unlikely that the applicant's proposed Vimovo tablet will cause any more significant harm or put patients in the general population at any greater risk of experiencing an adverse event than the currently marketed individual components.

Our risk-benefit analysis can not exclude some consideration of the patient's quality of life, which is inherently subjective and difficult to quantify. Gastrointestinal symptoms due to peptic ulcer disease can cause absenteeism or reduce productivity while at work, therefore causing wider implications for health care systems in terms of costs. It is highly probable that the patients that will benefit the most from Vimovo will have more than one medical condition and comorbidity. It is also probable that the ease of administering the two active components of Vimovo in one tablet will improve patient compliance and possibly patient outcomes. One can reasonably anticipate that Vimovo will be used chronically. At 6 months, the percentage of patients taking Vimovo who developed gastric ulcers was significantly lower than those taking Naproxen (5.6% vs. 23.7%). In the data that was submitted, overall rates of adverse events favored Vimovo (78.3%) over Naproxen® (87.6%). Although patients taking Vimovo experienced more cardiac events overall than placebo in the supportive trials (1.2% vs. 0%), the rate of cardiac adverse events was similar to the currently marketed Naproxen® (2.4% for Vimovo vs. 2.2% for Naproxen®). The 12 month long-term study did not show an increase in the rate of myocardial infarction (a known risk associated with NSAID use). Only 1 patient in the entire clinical development program experienced a myocardial infarction. Likewise, there does not appear to be an increase in the rate of cerebrovascular events. No patient in the clinical development program experienced a stroke. Three patients experienced a transient ischemic attack in the Vimovo group (0.25%). No one experienced a TIA in the control groups. Although there were no cases meeting criteria for Hy's Law, there were 2 cases of elevated hepatic enzymes > 10X the upper limit of normal. All of these side effects are known to be associated with either NSAID or PPI use and found in the current labeling for the respective components of Vimovo.

Nexium is only approved for 6 months for the risk reduction of NSAID induced ulcers. Prolonged use of PPIs has been associated with bacterial overgrowth, fractures, hypergastrinemia and other complications. (See Section 2.4) Although the naproxen component of Vimovo has two strengths (375mg and 500mg), the esomeprazole component of both dosage forms of Vimovo is fixed at 20mg. To ensure that the benefits of drug use outweigh the risks, the medical officer suggests that physicians consider daily use of this medication for no more than 6 months or use the lowest dose that will relieve patient symptoms for as short of a duration as possible. Additional recommendations for the safe use of this drug are reflected in the labeling section below.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

As of 2005, all prescription NSAIDs have been required to include a Box Warning and Medication Guide as parts of the product label due to the risk of cardiovascular and gastrointestinal adverse events. A Medication Guide only REMS is necessary to ensure that the benefits of Vimovo outweigh its risks of cardiovascular and gastrointestinal adverse events. These risks are included in the label of Vimovo and all members of the class of Nonsteroidal Anti-Inflammatory Drugs.

1.4 Recommendations for Postmarketing Requirements and Commitments

The sponsor has requested a full waiver from the requirement to conduct studies with Vimovo in patients from birth to 18 years of age. [REDACTED] (b) (4)

[REDACTED]. The proposed indication is for “the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk of developing NSAID-associated ulcers.” Essentially all patients on NSAID therapy are at risk of developing ulcers. In general the histology of pediatric gastric ulcers is similar to adults. While esomeprazole, a component of Vimovo, is approved for use in children as young as 1 year of age, there are no dosing recommendations for the sponsor’s proposed indication. Gastrointestinal toxicity from NSAIDs in children does exist but estimates of prevalence vary. Several papers using varying protocols and study participants have attempted to discern the prevalence of NSAID gastropathy in children, with varying conclusions. The percentage of pediatric patients who experience NSAID toxicity and the severity of the adverse effects in children appear to be less than that seen in adults. However, use of these medications on a chronic basis can still lead to potentially significant issues.¹

Juvenile Idiopathic Arthritis (previously known as juvenile rheumatoid arthritis) and other forms of inflammatory chronic arthritis represent the most frequently occurring indications for chronic use of NSAIDs in children.¹ No individual NSAID has been shown to have a clear advantage over others in treating arthritis or the fever associated with systemic arthritis.¹ Although it is difficult to determine the prevalence and incidence of the childhood arthropathies, approximately 300,000 children in the United States are estimated to have some type of arthritis.² Studies have been performed successfully in pediatric patients with JIA to establish a treatment indication. Naproxen is currently available in a suspension form for the treatment of JRA and seems to be the standard NSAID of choice in the pediatric rheumatology community.³

Although a COX-2 inhibitor, is an available option for pediatric patients on NSAIDs who require gastro-protective therapy, having additional options for children with JIA and those who do not respond to other therapies would be beneficial. Pediatric health care providers may also welcome an additional alternative NSAID preparation that decreases GI toxicity and perhaps has less potential for adverse events.

A pediatric consult was obtained. On April 14, 2010, the medical officer's recommendation for deferral of pediatric studies was presented to the Pediatric Review Committee. The PeRC committee concurred with the opinion of the review team. The efficacy of Vimovo tablets for juvenile arthritis and peptic ulcer disease can be extrapolated from the current data available for adults. Trials for patients under the age of 1 year will be waived because the disease does not occur in this age group and trials would be highly impractical. Trials for pediatric patients ages 2 years through 16 years will be conducted to establish safety and dosing.

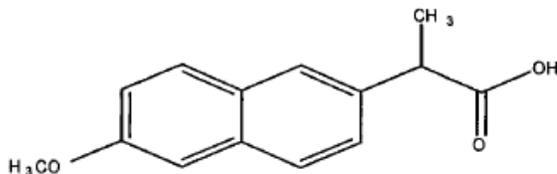
2 Introduction and Regulatory Background

2.1 Product Information

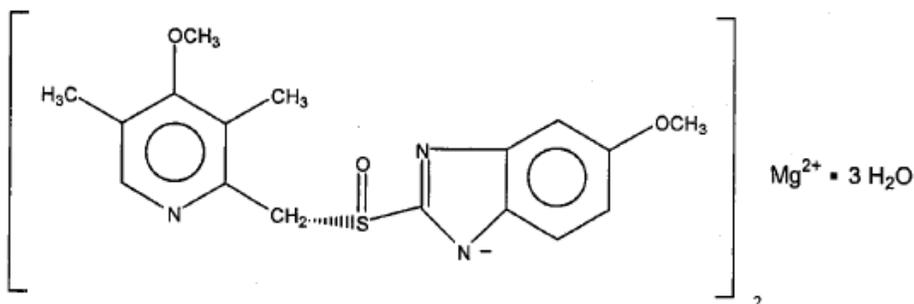
The sponsor has proposed the trade name Vimovo for this new combination NSAID/PPI. Vimovo is a fixed dose combination tablet containing either 375 mg or 500 mg of enteric coated delayed-release Naproxen in the core surrounded by 20 mg Esomeprazole (as the magnesium trihydrate salt) in the film coat. Both components are considered active ingredients. Per the sponsor, the tablets are formulated to release esomeprazole immediately followed by the delayed release of naproxen.

The chemical name for Naproxen is (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid. The chemical name for Esomeprazole magnesium is bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) Methyl] sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. The molecular formula for Naproxen is $C_{14}H_{14}O_3$. The molecular formula for the Esomeprazole magnesium component is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3 H_2O$. The structural formulas for each component are represented by the following diagrams:

Naproxen - (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid



Esomeprazole magnesium – bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate



The sponsor has requested the following 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the U.S and worldwide for the treatment of arthritis and other rheumatologic disorders.^{4,5} However, the use of NSAIDs is limited by their association with mucosal injury to the upper gastrointestinal (GI) tract.⁵ (Lower GI clinical events may also occur with NSAIDs but they are less common and less well studied than upper GI events.) It is estimated that between 15% to 30% of participants using NSAIDs regularly will develop ulcer disease and 2% to 4% will bleed or perforate^{5,6} Important risk factors for GI complications associated with NSAIDs include older age, prior history of upper GI event, use of corticosteroids or anticoagulants, and use of high-dose or multiple NSAIDs.^{2,6}

There are currently three products approved for the risk reduction of NSAID-associated gastric ulcers: Esomeprazole, Lansoprazole, and Copackaged Lansoprazole and Naproxen.

Table 1 Products Approved for the Risk Reduction of NSAID-associated Gastric Ulcers[#]

Product	NDA	Sponsor	Indication
Nexium (esomeprazole)	21-153 (capsule) 21-957 (suspension)	Astra Zeneca	“Reduction in the occurrence of GUs associated with continuous NSAID therapy in participants at risk for developing gastric ulcers. Participants are considered to be at risk due to their age (> 60) and/or documented history of GUs. Controlled studies do not extend beyond 6 months.”
Prevacid (lansoprazole)	20-406 (capsules) 21-281 (suspension) 21-428 (tablets)	TAP	“Reducing the risk of NSAID-associated GUs in participants with a history of a documented GU who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.”
Prevacid Naprapac (lansoprazole and naproxen)	21-507 (tablets)	TAP	“Reducing the risk of NSAID-associated GUs in participants with a history of documented GUs who require the use of an NSAID for treatment of the signs and symptoms of RA, OA, and/or AS. Controlled studies did not extend beyond 12 weeks.

Reviewer's Table

[#] RA, OA, AS and GU are rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gastric ulcers respectively.

The following tables list drugs that have been approved for either the treatment of Osteoarthritis, Rheumatoid Arthritis, or Ankylosing Spondylitis.

Table 2 Drugs Approved for the Treatment of Osteoarthritis and/or Rheumatoid Arthritis

Product	NDA	Sponsor	Indication
Anaprox/Anaprox DS (Naproxen Sodium)	018164	Roche	For the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis; For the relief of the signs and symptoms of tendonitis, bursitis, acute gout; For the management of pain and of primary dysmenorrhea
Naprosyn/EC Naprosyn (Naproxen)	017581 018965 020067	Roche	For the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis; For the relief of the signs and symptoms of tendonitis, bursitis, acute gout; For the management of pain and of primary dysmenorrhea Naprosyn Suspension is recommended for juvenile rheumatoid arthritis. EC Naprosyn is NOT recommended for initial treatment of acute pain.
Celebrex (Celecoxib)	020998 021156	Searle	Osteoarthritis Rheumatoid Arthritis (RA) Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older Ankylosing Spondylitis Acute Pain Primary Dysmenorrhea Familial Adenomatous Polyposis (FAP)
Clinoril (Sulindac)	017911	Merck	Acute or Long-term use in the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder (acute subacromial bursitis/supraspinatus)

			tendonitis) acute gout arthritis
Indocin (Indomethacin Indomethacin Sodium)	018332 0188878 018332	Merck	Has been found effective in the active stages of: moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; moderate to severe osteoarthritis; acute painful shoulder (bursitis and/or tendonitis) acute gouty arthritis
Voltaren (Diclofenac Sodium)	019201 022122	Novartis	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. For acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis
Mobic (Meloxicam)	020938 021530	Boehringer Ingelheim	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older
Nalfon (Fenoprofen Calcium)	0170604	Pedinol	Relief of mild to moderate pain in adults Relief of signs and symptoms of rheumatoid arthritis Relief of signs and symptoms of osteoarthritis
Enbrel for Injection (Etanercept)	(BLA) 103795	Immunex	Moderately to severely active Rheumatoid Arthritis (RA) Psoriatic Arthritis Ankylosing Spondylitis Chronic, moderate to severe psoriasis Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (JIA) in children 2 years and older

Table 3 Drugs Approved for the Treatment of Ankylosing Spondylitis

Product	NDA	Sponsor	Indication
Anaprox (Naproxen Sodium)	018164	Roche	For the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis; For the relief of the signs and symptoms of tendonitis, bursitis, acute gout; For the management of pain and primary dysmenorrhea
Celebrex (Celecoxib)	020998 021156	Searle	Osteoarthritis Rheumatoid Arthritis (RA) Juvenile Rheumatoid Arthritis (JRA) in patients 2year and older Ankylosing Spondylitis Acute Pain Primary Dysmenorrhea Familial Adenomatous Polyposis (FAP)
Clinoril (Sulindac)	017911	Merck	Acute or Long-term use in the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) acute gout arthritis
Naprosyn (Naproxen)	017581 018965 020067	Roche	For the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis; For the relief of the signs and symptoms of tendonitis, bursitis, acute gout; For the management of pain and of primary dysmenorrhea Naprosyn Suspension is recommended for juvenile rheumatoid arthritis. EC Naprosyn is NOT recommended for initial treatment of acute pain.
Enbrel for Injection (Entanercept)	(BLA) 103795	Immunex	Moderately to severely active Rheumatoid Arthritis (RA) Psoriatic Arthritis Ankylosing Spondylitis Chronic, moderate to severe psoriasis Moderately to severely active Polyarticular Juvenile Idiopathic

			Arthritis (JIA) in children 2 years and older
Humira Injection (Adalimumab)	(BLA) 125057	Abbott	Rheumatoid Arthritis Juvenile Idiopathic Arthritis Psoriatic Arthritis Ankylosing Spondylitis Crohn's Disease Plaque Psoriasis
Indocin (Indomethacin)	018332 0188878 018332	Merck	Has been found effective in the active stages of: moderate to severe Rheumatoid Arthritis including acute flares of chronic disease; moderate to severe Ankylosing Spondylitis; moderate to severe Osteoarthritis; acute painful shoulder (bursitis and/or tendonitis) acute gouty arthritis
Remicade for IV Injection (Infliximab)	(BLA) 103772	Centocor	Rheumatoid Arthritis Crohn's Disease Ankylosing Spondylitis Psoriatic Arthritis Plaque Psoriasis Ulcerative Colitis
Simponi Injection (Golimumab)		Centocor Ortho Biotech	Rheumatoid Arthritis (in combination with Methotrexate) Psoriatic Arthritis (alone or in combination with Methotrexate) Ankylosing Spondylitis
Voltaren (Diclofenac Sodium)	NDA 109201	Novartis	For relief of the signs and symptoms of Osteoarthritis and Rheumatoid Arthritis. For acute or long-term use in the relief of signs and symptoms of Ankylosing Spondylitis

Reviewer's Table

2.3 Availability of Proposed Active Ingredient in the United States

Both esomeprazole and naproxen have been marketed for a number of years in the United States. Pharmacologically, naproxen is a non-selective nonsteroidal anti-inflammatory drug that was first approved for marketing in the US in 1976. Naproxen is currently marketed in the US by several generic manufacturers and by Roche Pharmaceuticals under the trade names Naprosyn®, EC-Naprosyn®, Anaprox® and Anaprox DS®. It is indicated for the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis and acute gout. Some formulations are also indicated for the management of pain and primary dysmenorrhea. (Note: EC-Naprosyn® is not recommended for initial treatment of acute pain because the absorption is delayed compared to absorption from other naproxen-containing products.)

Esomeprazole belongs to the class of antisecretory compounds characterized pharmacologically as proton pump inhibitors. Esomeprazole is currently available in the U.S. as a prescription medicine for the treatment of symptomatic gastroesophageal reflux disease (GERD); short-term treatment in the healing and symptomatic resolution of erosive esophagitis; to maintain symptom resolution and healing of erosive esophagitis; the risk reduction of NSAID-associated gastric ulcer; *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Esomeprazole is marketed by AstraZeneca as Nexium®.

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling of all NSAID products includes a Medication Guide and a Boxed Warning highlighting the potential for increased risk of cardiovascular events and the serious potentially life-threatening gastrointestinal bleeding associated with their use.

Traditional NSAIDs may cause upper and lower GI tract mucosal injury. This is the main factor that limits the use of NSAIDs. Ulcers are found on endoscopy in 15 to 30% of patients using NSAIDs regularly.⁶ The annual incidence of upper GI complications (i.e. bleeding, perforation, and obstruction) is approximately 1.0% to 1.5%, whereas the annual rate of upper GI clinical events (complicated plus symptomatic uncomplicated ulcers) is approximately 2.5% to 4.5%.⁶ Although any patient taking NSAIDs is at risk of developing GI toxicity, several risk factors have been identified that, when present, increase the risk for upper GI clinical events. By current American College of Gastroenterology guidelines, these risk factors are prior clinical event, older age (>65 years), concomitant use of anticoagulation, corticosteroids, and low dose aspirin use.⁶

Administration of a NSAID may also cause a dose dependent reduction in prostaglandin synthesis and reduce renal blood flow, which may precipitate renal

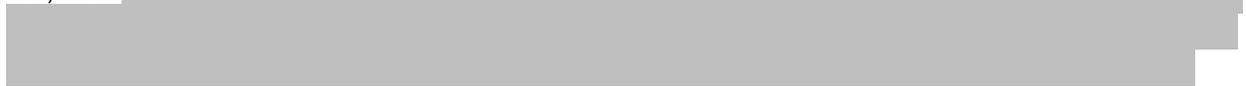
decompensation. Additionally, there have been concerns raised regarding the potential cardiovascular hazards of cyclooxygenase (COX)-2 inhibitors and other NSAIDs. The cardiovascular safety of individual NSAIDs is highly controversial particularly in participants with serious coronary heart disease.⁷ One COX-2 inhibitor was withdrawn from the U.S. market after it was found to be associated with an increase risk of heart attack and stroke. The mechanism of action for these adverse events may have been a coxib induced imbalance in circulating thromboxane (TXA₂) and prostacyclin (PGI₂) levels. Prostacyclin and thromboxane are derived from prostaglandin H₂. Prostacyclin causes vasodilation and inhibits platelet aggregation, whereas thromboxane causes vasoconstriction and promotes platelet aggregation. An increase in the ratio of thromboxane to prostacyclin could lead to increased platelet aggregation and dysregulation of platelet homeostasis.

Although current labeling for the six proton pump inhibitors (PPIs) approved for use in the US acknowledge common adverse reactions (i.e. headache, abdominal pain, nausea, vomiting, flatulence and diarrhea), the class of drugs is generally very well tolerated. Current labeling of esomeprazole also states that the PPI may increase INR and prothrombin time when administered concomitantly with warfarin. Additionally esomeprazole may interfere with the absorption of drugs for which gastric pH is an important determinant of their bioavailability and those drugs metabolized by the cytochrome P450 pathways. Current labeling of esomeprazole recommends that a dose of 20mg should not be exceeded for patient with severe liver impairment

Some studies have suggested that PPI therapy, particularly when given long-term and/or in high doses, is associated with several potential adverse effects, including enteric infections and community acquired pneumonia due to bacterial overgrowth.⁸ Other potential areas of concern regarding long-term proton pump inhibitor use have included carcinoid formation; development of gastric adenocarcinoma, and malabsorption of fats, minerals, and vitamins, especially vitamin B₁₂.^{8,10} There have also been concerns about rebound acid secretion following PPI discontinuation leading to dependency on the drug.⁸ Recently in the literature there has been discussion about a potential increase risk of hip fractures with prolonged PPI therapy.⁹ Another issue of interest has been a possible increase risk of adverse cardiovascular events when proton pump inhibitors are administered concurrently with clopidogrel (Plavix).¹⁰

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This NDA is being submitted under section 505(b)(2) of the Federal Food Drug and Cosmetic act. The sponsor conducted studies for the current application under IND 76,301. (b) (4)



The first protocol under IND 76,301 for PN400 tablets (later known as Vimovo tablets) was originally submitted March 2, 2007, and received on March 5, 2007. After initial review, the protocol was deemed safe to proceed. However the following recommendations and requests for information were made by the reviewer:

- The sponsor was asked to exclude participants with a history of ischemic heart disease, cardiac arrhythmia, heart failure, cerebrovascular disease, uncontrolled hypertension, peripheral atherosclerotic occlusive disease, thrombophlebitis, gastrointestinal ulceration, renal insufficiency, bleeding disorders and diabetes
- The sponsor was asked to exclude potentially confounding medications, such as ACE-inhibitors, antacids, sucralfate, cholestyramine, diuretics, lithium, methotrexate, and warfarin, from the study.
- The sponsor was advised that the Naproxen black box warning regarding cardiovascular and gastrointestinal risks should be included in the informed consent. The sponsor was also asked to provide a copy of the informed consent with the protocol.
- The sponsor was asked to exclude participants from the trial with abnormal ECG at the screening visit.
- The sponsor was asked to exclude subjects with abnormal urinalysis at the Screening.
- The sponsor was asked to revise the protocol by adding stopping rules for individual participants and the entire study.
- The sponsor was asked to conduct animal safety studies using the combination tablet and submit the results for review prior to initiation of Phase III clinical trials.

On May 16, 2007, the Agency received correspondence from the sponsor requesting a Type B, End-of-Phase 2 meeting. The background package from that meeting was received June 12, 2009. After preliminary responses were faxed to the sponsor on July 9, 2007, the sponsor requested additional clarification to the responses but agreed to cancel the meeting that was scheduled for July 12, 2007. A summary of the revised responses are below:

- The primary endpoint to support the proposed claim for the risk reduction of NSAID-associated ulcers should be the proportion of participants who develop gastric ulcer.
- The sponsor will need to address an appropriately defined high risk population to preclude exclusionary language with regard to high risk participants in the label. However, the Agency was unable to confirm that the sponsor's proposed high risk population was adequate.
- The sponsor will need to conduct bioequivalence studies for the esomeprazole component. Additionally the sponsor will need to

demonstrate that all chemical properties and physical properties of the tablets from both manufacturing sites are comparable. This includes a comparison of the dissolution profiles for tablets, demonstrating comparable immediate release properties of esomeprazole and delayed release properties of the naproxen.

The Pre-NDA Meeting for this submission occurred March 23, 2009. In attendance were members from the Division of Anesthesia, Analgesia and Rheumatology Products, the Division of Gastroenterology Products, and the Office of Surveillance and Epidemiology. A summary of the discussion and agreements from that meeting are as follows:

- The Safety plan will focus on the overall treatment emergent adverse events, deaths, serious adverse events (SAEs), adverse events (AEs) leading to study discontinuation, laboratory results, vital signs and physical examination findings. In addition, treatment emergent adverse events will also be summarized by demographics, baseline risk factors and drug exposure. All adverse events are coded with MedDRA 10.1.
- For the GI Division, it was agreed that the sponsor's Integrated Summary of Efficacy would include findings from 2 adequate and well controlled pivotal trials whose primary endpoint would be Cumulative Incidence of Gastric Ulcers at 6 months.
- It was also agreed that sponsor would perform exploratory statistical comparisons for key primary efficacy endpoints by subgroups. "Key Primary Efficacy Endpoint by Subgroups" refers to the following: age greater than 65years, age less than 65yrs, low dose Aspirin in ages greater than or equal to 50 years, gender, and smoking status.
- The sponsor was asked to provide a comparative summary of Esophageal events (esophageal stenosis and esophageal ulcer), Gastric events (specifically GI hemorrhage, GI erosions) and Duodenal hemorrhages
- In terms of the analgesic efficacy of the new drug, it was agreed that "Substantial evidence of analgesic efficacy of PN400 will rely on analysis of data from 2 controlled individual trials where the primary endpoint to support a finding of efficacy would be the changes from baseline to the end of treatment in WOMAC Pain and Function Scores and patient Global Assessment."
- It was agreed that additional evidence of analgesic efficacy will be based on Bioequivalence of the new drug to EC-Naprosyn.
- The sponsor (b) (4) was advised that due to the fact that Naproxen is approved for Juvenile Rheumatoid Arthritis (JRA), the pediatric development plan should be submitted with the NDA.

2.6 Other Relevant Background Information

On January 29, 2009, the Office of Compliance determined that one of the site investigators, Dr. Howard Marker, submitted false information to the sponsor. Dr. Marker was responsible for 3 participants in Protocol PN400-301 conducted under IND 76,301 (2 participants in the Vimovo arm and 1 patient in the Naproxen arm)

3 Ethics and Good Clinical Practices

Per the sponsor, all studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, as well as described in the Code of Federal Regulations, Title 21, Part 50 (21CFR50).

3.1 Submission Quality and Integrity

Overall the quality of the submission was acceptable in terms of data organization, retrieval, and completeness. There were some minor inconsistencies in the analyses prompting information requests from the sponsor. All sites were located in the United States. As stated previously, one of the sites (site 401 from trial PN400-301) was omitted from the analysis because the investigator was found to have submitted false information to the sponsor.

The Division of Scientific Investigations (DSI) conducted inspections on the 4 sites that enrolled the largest number of study participants. The four clinical investigator sites were inspected in support of the application as part of a routine data audit. Please see the completed review of Dr. Khairy Malek for greater details. In short, no regulatory violations were noted at two of the four sites. Although minor regulatory violations were noted at the other two sites, the inspector determined that these violations were unlikely to significantly impact data integrity and that the data generated from all 4 sites could be used in support of the NDA.

3.2 Compliance with Good Clinical Practices

Per the sponsor, the [REDACTED] (b) (4) served as the central IRB for trials PN400-301, PN400-302, PN400-304, by reviewing and approving the protocol, amendments and informed consents documents.

[REDACTED] (b) (4) served as the central IRB for trials PN400-307 and PN400-309. All trials were conducted in accordance with the ethical principles in the Declaration of Helsinki as well as described in 21 CFR.50. Each study participant was provided with written informed consent prior to participating in the trial.

For the clinical pharmacology studies, each site's investigational review board (IRB) reviewed and approved the protocol. Please see the clinical pharmacology reviews of Drs. Peifan Bai and Dilara Jappar for additional details.

3.3 Financial Disclosures

The applicant submitted signed copies of forms 3454 “Certification: Financial Interests and Arrangements of Clinical Investigators” certifying that no financial arrangement with the listed clinical investigators had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); also certifying that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product; and certifying that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). A complete list of all clinical investigators involved in the clinical trials was attached to the form.

The applicant also submitted a signed copy of form 3455 “Disclosure: Financial Interests and Arrangements of Clinical Investigators” for one investigator, (b) (4) in accordance with 21 CFR 54 disclosing details of the individual’s disclosable financial arrangements and interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

For additional details relevant to section 4, please see the reviews conducted by Drs. Rajiv Agarwal, Albert Chen, and Charles Wu.

4.1 Chemistry Manufacturing and Controls

The sponsor has proposed two strengths of Vimovo containing either 375 mg of enteric coated Naproxen or 500 mg of enteric coated Naproxen surrounded by 20 mg of immediate release esomeprazole magnesium. The drug product is an oval, yellow, film-coated tablet printed with either 375/20 or 500/20 in black on one side. Per the sponsor, the two strengths of PN400 are considered dose proportional.

The sponsor applied for categorical exclusion from the environmental assessment. Per CMC, this combination tablet NDA qualifies for a categorical exclusion from the requirement to submit an Environmental Assessment under 21CFR25.31(a).

4.2 Clinical Microbiology

This section is not applicable for the current application.

4.3 Preclinical Pharmacology/Toxicology

A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

Because this is a 505 (b)(2) application, no nonclinical safety studies were conducted with Vimovo tablets. It is noteworthy to mention that the esomeprazole of Vimovo tablets is not enteric coated. The sponsor noted that nonclinical toxicology programs supporting both omeprazole and esomeprazole were completed using non-enteric coated, unbuffered active ingredients. Additionally, a rat study was conducted to identify and characterize any new urinary and plasma degradants that may arise from the administration of the uncoated drug. Per the sponsor, no new degradants were observed.

The proposed clinical doses for the Vimovo tablets are consistent with currently approved and marketed doses of the individual components, naproxen and esomeprazole. The sponsor also provided published data to support the safety of the drug from a nonclinical standpoint. The combined administration of naproxen and esomeprazole is expected to demonstrate the known toxicity of each of the components. It is anticipated that no new types of toxicity or exacerbations of existing toxicities should result from the combined administration of naproxen and esomeprazole in one tablet.

Please see the pharm/tox review of Dr. Charles G. Wu for further details.

4.4 Clinical Pharmacology

Please see the reviews of Dr. Peifan Bai and Dr. Dilara Jappar for further information and details.

4.4.1 Mechanism of Action

Naproxen is a propionic acid derivative that reduces prostaglandin production and leukocyte activation by inhibiting the cyclooxygenase enzyme pathway. Consequently, use of the drug results in decreased inflammation, analgesia, and anti-pyretic activity.

Esomeprazole is a substituted benzimidazole that irreversibly inhibits the H⁺K⁺-ATPase pump in the gastric parietal cell reducing acid production.

4.4.2 Pharmacodynamics

In Phase I trials, the sponsor studied Vimovo tablets containing 10mg, 20mg, and 30mg doses of esomeprazole. Pharmacodynamic responses of pH control were evaluated in study PN400-104, evaluated by clinical pharmacology. The primary endpoint in this study was the percentage of time that intragastric pH was greater than 4.0. Direct measurement of protection against gastrointestinal lesions caused by naproxen administration, were evaluated using the Lanza score in PN400-101, also evaluated by clinical pharmacology.

Please see section 7.2 below for more information.

4.4.3 Pharmacokinetics

It is important to note that the naproxen core in Vimovo tablets is enteric coded, while the surrounding esomeprazole is not. As per the clinical pharmacology review, the 375 mg and 500mg dosages of the naproxen in Vimovo tablets is bioequivalent to the 375 mg and 500 mg dosages of EC-Naprosyn®. Because the 500mg/20mg dosage was used in the Phase III clinical trials, information on the pharmacokinetics of that dosage will be presented.

The mean C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and (T_{1/2}) half-life of the naproxen in the 500mg/20mg Vimovo tablet in healthy study participants were 66.9µg/ml, 6.15 hrs, 1226 hr*µg/ml, 1326 hr*µg, and 18.9hrs respectively.

The mean C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and (T_{1/2}) half-life of the esomeprazole in the 500mg/20mg Vimovo tablet in healthy study participants were 425 µg/ml, 0.51 hrs, 465

hr* μ g/ml, and 0.97hrs respectively. The area under the curve (AUC) for the 20mg dose of esomeprazole in Vimovo was 58% of that seen following administration of the 20mg dose of Nexium® (465 hr* μ g/ml versus 801hr* μ g/ml) on Day 1. This increased by Day 9. Reportedly there are no drug-drug interactions. Coadministration of the naproxen and esomeprazole did not alter the pharmacokinetic profile of either drug. When Vimovo was administered with a high-fat meal, the bioavailability of the esomeprazole was decreased by 50% and there was delayed absorption of the naproxen component. This was most likely due to increased acid production associated with high fat meals and lowering of the pH. Proton pump inhibitors are acid labile. Additionally the delayed release naproxen is dissolved at a (b) (4)

5 Sources of Clinical Data

The overall clinical development program enrolled study participants in 13 clinical trials. There were 2337 patients in the 6 Phase III trials and 214 normal healthy volunteers in the 7 Phase I trials. Trials PN400-301 and PN400-302 were designed to assess the efficacy of Vimovo tablets compared with Naproxen at reducing the incidence of gastric ulcers in patients requiring chronic NSAID use. Trials PN400-307 and PN400-309 were supportive studies that compared Vimovo with celecoxib and placebo at relieving the pain of osteoarthritis of the knee. Long term safety was demonstrated in trial PN400-304. The table below summarizes all of the studies and clinical trials submitted by the sponsor in support of the current application.

5.1 Table of Clinical Studies/Trials

Table 4 Table of Clinical Trials

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN400-301 (Pivotal)	Safety and Efficacy	Reduction of risk of gastric ulcers in at risk participants	Double-blind, Randomized, Parallel Group, Active Control Multicenter	500mg Naproxen/ 20mg Esomeprazole, tablet bid, 30 to 60 mins before food oral vs. 500mg Naproxen tablet bid, 30 to 60 mins before food, oral	400 Planned 438 Randomized 434 Treated 333 Completed	Pts with a history of OA, RA, ankylosing spondylitis or other medical conditions that require daily NSAID therapy	6 months
PN400-302 (Pivotal)	Safety and Efficacy	Reduction of risk of gastric ulcers at risk participants	Double-blind, Randomized, Parallel Group, Active Control Multicenter	500 mg Naproxen/ 20 mg Esomeprazole tablet, bid 30-60 mins before food oral vs. 500 mg Naproxen tablet bid, 30- 60 mins before food, oral	400 Planned 423 Randomized 420 Treated 304 Completed	Participants with history of OA, RA, ankylosing spondylitis or other medical conditions that require daily NSAID therapy	6 months

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN 400-303 (Terminated)	Safety and Efficacy in High Risk	Incidence of gastric ulcers in high risk population at 6 months	Double-blind, Randomized, Parallel Group, Active Controlled Multicenter	500mg Naproxen/20 mg Esomeprazole tablet oral bid vs. Over-encapsulated ATHROTEC® 75 capsules (75mg diclofenac sodium/200mcg misoprostol) oral bid	200 Planned 20 Randomized 3 Completed Study Terminated	Participants with history of OA, RA, ankylosing spondylitis or other medical conditions that require daily NSAID therapy, with history of documented serious upper gastrointestinal event such as perforation, obstruction or bleeding.	6 months (*Study terminated Study synopsis complete)

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN 400-304	Long-Term Safety	Long term safety of PN 400 in at risk participants	Open-label, multicenter	500mgNaproxen/20 mg Esomeprazole tablet oral bid	200 Planned 239 Randomized 239 Treated 143 Completed	Participants with a history of OA, RA, ankylosing spondylitis, or other medical conditions that require daily NSAID therapy	1 year
PN 400-307 (Pivotal Reviewed by DAARP)	Non-inferiority	Non-inferiority of PN 400 and celecoxib in treatment of signs and symptoms of OA	Double-blind, parallel group, randomized, active controlled, multicenter	500mg Naproxen/20 mg Esomeprazole tablet bid and placebo capsule qd oral 30 to 60 mins before meals. vs. Overencapsulated CELEBREX® (celecoxib) 200mg capsule qd and placebo tablet bid oral 30 to 60 mins before meals oral vs. Placebo tablet bid and placebo capsule qd, 30 to 60 mins before meals oral	570 Planned 619 Randomized 614 Treated 521 Completed	Participants with a history of OA of the knee that requires daily NSAID therapy	3 months

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN 400-309 (Pivotal Reviewed by DAARP)	Non-inferiority	Non-inferiority of PN 400 and celecoxib in treatment of signs and symptoms of OA	Double-blind, randomized, parallel group, active controlled, multicenter	500mg Naproxen/20 mg Esomeprazole tablet bid and placebo capsule qd oral 30 to 60 mins before meals. vs. Overencapsulated CELEBREX® (celecoxib) 200mg capsule qd and placebo tablet bid oral 30 to 60 mins before meals oral vs. Placebo tablet bid and placebo capsule qd, 30 to 60 mins before meals oral	570 Planned 615 Randomized 610 Treated 489 Completed	Participants with a history of OA of the knee that requires daily NSAID therapy	3 months

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN400-101	PK/PD	Gastric injury of various naproxen plus esomeprazole dose combinations and EC naproxen alone	Open-label, single-blind, randomized, parallel group	500 mg Naproxen, multiple & esomeprazole doses tablet bid, 60 mins prior to food, oral	80 Enrolled (20/arm) 77 Completed	Healthy Participants	14 days
PN400-102	BA/BE	Relative BA of naproxen in various treatments	Open-label randomized 3 way crossover	Two tablet formulations, 500mg Naproxen, EC NAPROSYN®, oral	36 Enrolled 29 Completed	Healthy Participants	Single Dose
PN400-103	Food Effect	Food effects on naproxen and esomeprazole BA from PN 400	Open-label randomized 4-way crossover	500mg Naproxen/20 mg Esomeprazole oral with food 30 and 60 mins prior to food, fasted,	24 Enrolled 21 Completed	Healthy Participants	Single Dose
PN400-104	PK/PD	PK/PD of various naproxen plus esomeprazole dose combinations and EC naproxen 500mg plus EC esomeprazole 20mg	Open-label randomized 4-way crossover	500mg Naproxen, multiple esomeprazole doses bid oral 60 mins prior to food	28 Enrolled 28 Completed	Healthy Participants	9 days

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN400-105	BA	Relative BA of naproxen in PN 400 (naproxen 375 mg/esomeprazole 20 mg)	Open-label, randomized, 2-way crossover	375mg Naproxen/20 mg Esomeprazole, vs. ECNAPROSYN® 375 mg tablet, oral Note: Naproxen is 375 mg in this Tablet	30 Enrolled 30 Completed	Healthy Participants	Single Dose
PN 400-106(D112 0C00007)	BA	Relative BA of celecoxib and overencapsulated celecoxib	Open-label, randomized, 2-way crossover	Celecoxib 200mg capsule vs. Overencapsulated Celecoxib 200mg capsule	90 Enrolled 87 Completed	Healthy Participants	Single Dose
PN400-111	PK	Intra-subject variability of esomeprazole PK	Open-label, 2-way crossover	500mg Naproxen/20 mg Esomeprazole tablet oral	18 Enrolled 17 Completed	Healthy Participants	Single dose and repeat daily bid doses for 10 days.

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

Trial Name	Trial Type	Objective	Trial Design	Treatment Product(s) Dosage Regimen; Route of Administration	Number Enrolled	Population	Duration of Treatment
PN400-114	BA/BE	BA of esomeprazole and BA of naproxen	Open-label, randomized, 4-way crossover	500 mg Naproxen/20 mg Esomeprazole tablet vs. 500 mg naproxen alone, vs. 20 mg esomeprazole alone and the combination, oral	24 Enrolled 24 Completed	Healthy Participants	5 days
PN200-105	PK/PD, Food Effect	Food effect on PN200, 500 mg naproxen and 20 mg omeprazole	Open-label, randomized, 3-way crossover	500 mg naproxen/20 mg Omeprazole tablet With food and 30 and 60 mins prior to food, bid, oral	24 Enrolled 24 Completed	Healthy Participants	5 days

Reviewer's Table

5.2 Review Strategy

To demonstrate that Vimovo prevents the development of ulcers in patients at risk for developing NSAID associated gastric ulcers, the sponsor submitted two pivotal studies (PN400-301 and PN400-302). Upon completion of the individual study review for efficacy, data from all trials submitted in support of this application were reviewed and combined into an integrated safety evaluation.

In support of this application, the sponsor submitted two 3- month Phase III clinical trials (PN400-307 and PN400-309) to demonstrate that Vimovo was superior to placebo and non-inferior to celecoxib for relief of pain associated with osteoarthritis of the knee. These two trials were evaluated by the Division of Anesthesia, Analgesia, and Rheumatology. Please see the review of Dr. Jin Chen for greater detail.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Overview of Protocols Submitted with Application

The applicant submitted 5 Phase III clinical trials in support of the efficacy and safety of this new combination drug. One trial, PN400-303, was discontinued due to problems with enrollment. The other four trials (PN400-301, PN400-302, PN400-307 and PN400-309) were submitted in support of Vimovo's safety and efficacy for the claimed indication. The sponsor also submitted data from one long-term safety trial, PN400-304, to support the safety of the Vimovo tablets.

Trials PN400-307 and PN400-309 will be reviewed by the medical officer from the Division of Anesthesia, Analgesia, and Rheumatology Products. Please see the consult of Dr. Jin Chen for further details. This efficacy review focused on trials PN400-301 and PN400-302. Both studies were identically designed to demonstrate the effectiveness of Vimovo in reducing the risk of gastric ulcers in participants at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers. There were 2 protocol amendments to each study. The tables below provide a Summary of the Trial Protocols for studies PN400-301, PN400-302, and PN400-307. For greater details, please see Appendix 9.4.

Table 5 Reviewer's Summary of Trial Protocol PN400-301

<i>Study # and Period</i>	PN400-301 (August 2007 – August 2008)
<i>Design</i>	6 month, Phase 3, Randomized, Double-Blind, Parallel-Group, Active Controlled, Multicenter Study (60 sites)
<i>Primary Objectives</i>	To demonstrate that Vimovo is effective in reducing the risk of gastric ulcers in participants at risk for developing NSAID-associated gastric ulcers
<i>Secondary Objectives</i>	To determine if Vimovo is effective in risk reduction of duodenal ulcers in participants at risk for developing NSAID-associated ulcers. To compare upper GI symptoms (measured by scored on the SODA: Severity of Dyspepsia Assessment and OTE-DP: Overall Treatment Evaluation-Dyspepsia instruments) in participants treated with Vimovo vs. Naproxen To compare heartburn symptoms between Vimovo vs. Naproxen To evaluate the safety and tolerability of Vimovo and Naproxen
<i>Treatments</i>	Vimovo (Naproxen 500mg/Esomeprazole 20mg) twice daily vs. Enteric Coated Naproxen 500 twice daily
<i>Sample Patient Population</i>	Adults (≥18yo) with a medical condition expected to require daily NSAID therapy for at least 6 months AND < 50yo have a documented history of gastric or duodenal ulcer within the past 5 years. All were <i>H. pylori</i> -negative and did not have a gastric or duodenal ulcer at Baseline.
<i>Number Planned (Number Enrolled)</i>	400 (200 per treatment group) planned 438 Randomized 434 Received Study Medication 218 Vimovo 216 EC Naproxen
<i>Efficacy Data</i>	Gastroduodenal Endoscopy at Screening, 1, 3, and 6 month visits Patient Reported Outcomes (PRO) as measured by score on the SODA and OTE-DP instruments throughout the trial
<i>Primary Efficacy Parameters</i>	<ul style="list-style-type: none"> Proportion of participants developing gastric ulcers throughout the 6 months of study treatment. (Treatment groups were compared using a CMH test stratified by use of low-dose aspirin at randomization) Time to development of gastric ulcers. (A log-rank test stratified by use of low-dose aspirin at randomization was used to test the difference between treatment groups in the survival curves)
<i>Key Secondary Efficacy Parameters</i>	<ul style="list-style-type: none"> Incidence of duodenal ulcers at any time throughout 6 months of treatment.
<i>Safety Data</i>	Adverse events (AEs), Serious AEs (SAEs), Clinical Laboratory evaluations, Vital Signs and Physical Examinations
<i>Key Tolerability Parameters</i>	The proportion of participants with UGI AEs or duodenal ulcers. The proportion of participants discontinuing the study due to UGI AEs or due to duodenal ulcers.
<i>Protocol Amendment 1</i>	Date: September 17, 2007

	<p>Purpose: To update the Emergency Contact Information To include the term “non-breastfeeding” in the Inclusion Criteria To modify wording regarding pregnancies occurring during the study to include pregnancies in partners of male subjects To modify the period of time that study participants are not allowed to use a PPI, H2 blocker, or sulcrafate To clarify the definition of a “completed subject” so that a participant is considered to have completed the study if either of the following criteria is met 1) completion of 6 months of study drug treatment and the 6 month endoscopy OR 2) endoscopic confirmation of a gastric ulcer at any time during study drug treatment including at the 6 month visit. (If a duodenal ulcer is detected at anytime during the study drug treatment, including the 6th month visit, the participant will be withdrawn and will not be considered as completing the study. To clarify the dispensing of acetaminophen and antacid To modify recording of study drug dispensation To provide guidance on issuing numbers to participants who are re-screened.</p>
<p><i>Protocol Amendment 2</i></p>	<p>Stamp Date: June 17, 2008 Purpose: To modify the “other” objectives to include an assessment of the effect of concomitant low-dose aspirin use on the incidence of <u>gastroduodenal ulcers</u> within each treatment group. To modify efficacy variables to include “the incidence in gastroduodenal ulcers at any time throughout 6 months of treatment by low-dose aspirin use at randomization (Yes/No). To update the exclusion criteria to exclude participants who had previously participated in a PN400 (aka Vimovo) study. To update the statistical analysis section, modifying wording regarding acetaminophen and antacid and add clarification on AE and concomitant medication recording. (Note the final statistical analysis plan for Study PN400-301 is identical to the statistical analysis plan for Study PN400-302.)</p>

Table 6 Reviewer's Summary of Trial Protocol PN400-302

<i>Study # and Period</i>	PN400-302 (September 21, 2007 – September 29, 2008)
<i>Design</i>	6 month, Phase 3, Randomized, Double-Blind, Parallel-Group, Active Controlled, Multicenter Study (60 sites)
<i>Primary Objectives</i>	To demonstrate that Vimovo is effective in reducing the risk of gastric ulcers in participants at risk for developing NSAID-associated gastric ulcers
<i>Secondary Objectives</i>	To determine if Vimovo is effective in risk reduction of duodenal ulcers in participants at risk for developing NSAID-associated ulcers. To compare upper GI symptoms (measured by scored on the SODA: Severity of Dyspepsia Assessment and OTE-DP: Overall Treatment Evaluation-Dyspepsia instruments) in participants treated with Vimovo vs. Naproxen To compare heartburn symptoms between Vimovo vs. Naproxen To evaluate the safety and tolerability of Vimovo and Naproxen
<i>Other Objectives</i>	To assess the effect of concomitant use of low-dose aspirin ($\leq 325\text{mg}$) on the incidence of ulcers in each treatment arm
<i>Treatments</i>	Vimovo (Naproxen 500mg/Esomeprazole 20mg) twice daily vs. Enteric Coated Naproxen 500 twice daily
<i>Sample Patient Population</i>	Adults ($\geq 18\text{yo}$) with a medical condition expected to require daily NSAID therapy for at least 6 months AND $< 50\text{yo}$ have a documented history of gastric or duodenal ulcer within the past 5 years. All were <i>H. pylori</i> -negative and did not have a gastric or duodenal ulcer at Baseline.
<i>Number Planned (Number Enrolled)</i>	400 planned (200 per treatment group) 423 randomized 420 received study medication (Analyzed for efficacy) 210 Vimovo 210 Naproxen 304 completed the study
<i>Efficacy Data</i>	Gastroduodenal Endoscopy at Screening, 1, 3, and 6 month visits Patient Reported Outcomes (PRO) as measured by score on the SODA and OTE-DP instruments throughout the trial
<i>Primary Efficacy Parameters</i>	Proportion of participants developing gastric ulcers throughout the 6 months of study treatment. (Treatment groups were compared using a CMH test stratified by use of low-dose aspirin at randomization) Time to development of gastric ulcers. (A log-rank test stratified by use of low-dose aspirin at randomization was used to test the difference between treatment groups in the survival curves)
<i>Key Secondary Efficacy</i>	Incidence of duodenal ulcers at any time throughout 6 months of treatment.

Clinical Review of Safety and Efficacy
 Erica L. Wynn, MD MPH
 NDA 022511
 Vimovo Naproxen/Esomeprazole Magnesium

<i>Parameters</i>	
<i>Safety Data</i>	Adverse events (AEs), Serious AEs (SAEs), Clinical Laboratory evaluations, Vital Signs and Physical Examinations
<i>Key Tolerability Parameters</i>	The proportion of participants with UGI AEs or duodenal ulcers. The proportion of participants discontinuing the study due to UGI AEs or due to duodenal ulcers.
<i>Protocol Amendment 1</i>	Date: September 17, 2007 Purpose: To update the Emergency Contact Information To include the term “non-breastfeeding” in the Inclusion Criteria To modify wording regarding pregnancies occurring during the study to include pregnancies in partners of male subjects To modify the period of time that study participants are not allowed to use a PPI, H2 blocker, or sulcrafate To clarify the definition of a “completed subject” so that a participant is considered to have completed the study if either of the following criteria is met 1) completion of 6 months of study drug treatment and the 6 month endoscopy OR 2) endoscopic confirmation of a gastric ulcer at any time during study drug treatment including at the 6 month visit. (If a duodenal ulcer is detected at anytime during the study drug treatment, including the 6 th month visit, the participant will be withdrawn and will not be considered as completing the study. To clarify the dispensing of acetaminophen and antacid To modify recording of study drug dispensation To provide guidance on issuing numbers to participants who are re-screened.
<i>Protocol Amendment 2</i>	Stamp Date: June 17, 2008 Purpose: To modify the “other” objectives to include an assessment of the effect of concomitant low-dose aspirin use on the incidence of <u>gastroduodenal ulcers</u> within each treatment group. To modify efficacy variables to include “the incidence in gastroduodenal ulcers at any time throughout 6 months of treatment by low-dose aspirin use at randomization (Yes/No). To update the exclusion criteria to exclude participants who had previously participated in a PN400 (aka Vimovo) study. To update the statistical analysis section, modifying wording regarding acetaminophen and antacid and add clarification on AE and concomitant medication recording. (Note the final statistical analysis plan for Study PN400-301 is identical to the statistical analysis plan for Study PN400-302.)

Table 7 Reviewers Summary of Trial Protocol PN400-304

<i>Study # and Period</i>	PN400-304 (October 2007 – March 2009)
<i>Design</i>	12 month , Phase 3, Open-label, multi-center (Approximately 60 sites), trial of PN-400 in subjects at risk for developing NSAID-associated ulcers
<i>Primary Objectives</i>	To evaluate the long-term safety of PN400 in participants at risk for developing NSAID-associated upper GI ulcers
<i>Secondary Objectives</i>	None
<i>Treatments</i>	Vimovo (delayed-release Naproxen 500mg/ Immediate release Esomeprazole 20mg) twice a day for 1 year.
<i>Sample Patient Population</i>	Adult (≥18yo) male or non-pregnant female with a history of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or other medical condition expected to require daily NSAID therapy for at least 12 months who are at risk for developing NSAID-associated gastric ulcers.
<i>Number Planned (Number Enrolled)</i>	200 patients planned 239 enrolled and treated 143 completed the study
<i>Efficacy Data</i>	Not Applicable
<i>Primary Efficacy Parameters</i>	Not Applicable
<i>Key Secondary Efficacy Parameters</i>	Not Applicable
<i>Safety Data</i>	Endoscopy results, physical examination, vital signs, ECGs, laboratory tests,
<i>Key Tolerability Parameters</i>	Adverse Events, Laboratory tests, Physical Examination, Vital Signs, and Electrocardiograms (ECGs)

5.3.2 Clinical Overview of Trial PN400-301

Additional information is provided in Section 6 below. There were 218 study participants in the Vimovo arm and 216 in the Naproxen arm. Summaries of demographic and baseline characteristics below are based on the ITT population. Baseline characteristics for both treatment arms of the study were similar. For both arms the population was predominantly White (approximately 84%), Non-Hispanic (78-79%), and female (69%). The mean age for the Vimovo group was 60.8 years and 61.9 years for the Naproxen group. Approximately 24% of study participants in each arm used low-dose aspirin. Roughly 5% of study participants in both arms had a documented history of a gastric ulcer and roughly 6% study participants in both arms reported a history of an ulcer within the 5 previous years. The majority of patients in both arms were using NSAIDs because of a diagnosis of osteoarthritis.

Table 8 Baseline Demographics Trial PN400-301 (ITT Population)

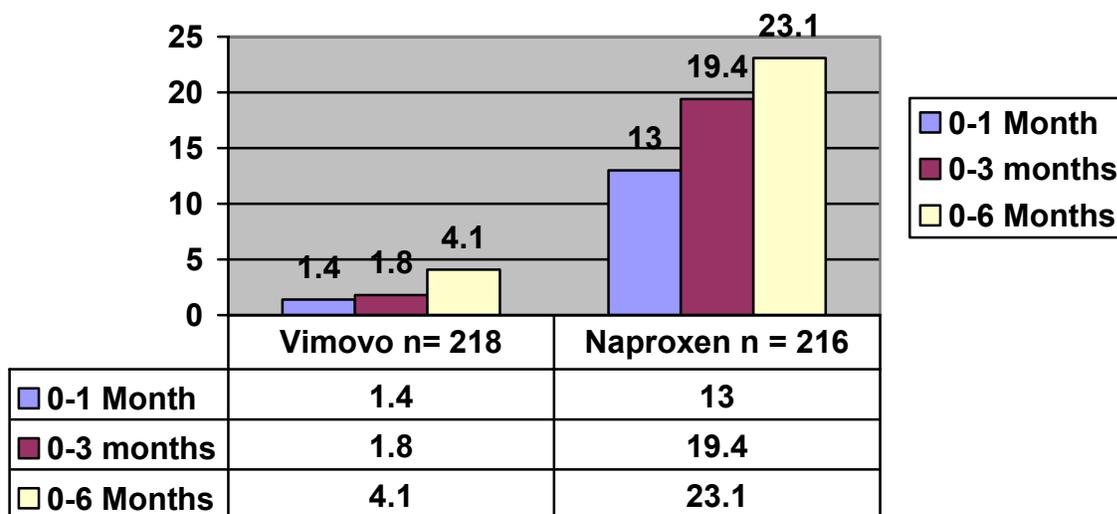
	PN400-301 (n = 434)	
Characteristic	Vimovo (n = 218)	Control (n = 216)
Age (years):		
Mean (std)	60.8 (8.8)	61.9 (8.5)
Median	60.0	61.0
Min, Max	30, 90	43, 90
Age Group:		
< 60	105 (48.2%)	97 (44.9%)
<50	6 (2.8%)	3 (1.4%)
50-59	99 (45.4%)	94 (43.5%)
≥ 60	113 (51.8%)	119 (55.1%)
Sex		
Male	68 (31.2%)	67 (31.0%)
Female	150 (68.8%)	149 (69.0%)
Race		
White	184 (84.4%)	81 (83.8%)
Black	27 (12.4%)	32 (14.8%)
Asian	4 (1.8%)	2 (0.9%)
Ethnicity		
Hispanic/Latino	5 (20.6%)	47 (21.8%)
Not	173 (79.4%)	169 (78.2%)

Hispanic/Latino		
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For efficacy the sponsor defined the Intent-to-treat (ITT) population as all randomized subjects who received at least 1 dose of study drug and had no ulcer detected by endoscopy at the Screening Visit. The Per-protocol (PP) population was all subjects in the ITT population who did not violate the protocol in any major way that would have impacted the evaluation of efficacy and had at least 70% overall treatment compliance. Subjects excluded from the per-protocol population were identified prior to unblinding of the treatment code. All efficacy and safety analyses were based on the ITT population. Primary and key secondary efficacy and safety analysis were also analyzed using the PP population.

For both the ITT and PP populations, the cumulative incidence in gastric ulcers was lower in patients in the Vimovo treatment group relative to the Naproxen group. This difference was statically significant. This finding was seen as early as 1 month and persisted at 3 and 6 months. The following figure provides a summary of the analysis of the cumulative observed incidence of gastric ulcers at 1, 3, and 6 months for the ITT population.

Figure 1 Cumulative Observed Incidence of Patients Developing Gastric Ulcers at 1, 3, and 6 Months Trial PN400-301 ITT Population (Percentages Reported)



At 1 month 1.4% of patients in the Vimovo group compared to 13.0% of patients in the Naproxen group developed a Gastric Ulcer. At 3 months, 1.8 percent of patients taking Vimovo versus 19.4% of patients taking Naproxen developed gastric ulcers. At 6

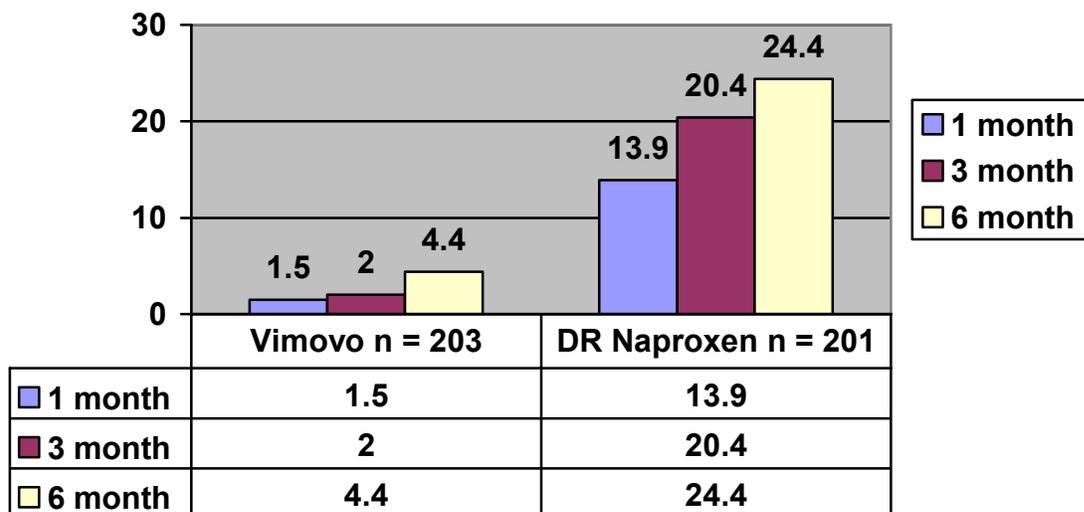
months 4.1% of the patients in the Vimovo group developed a gastric ulcer as opposed to 23.1% of patients in the Naproxen group. These results are statistically significant. The following table provides the actual numbers for the graphic depicted above.

Table 9 Cumulative Incidence of Patients Developing Gastric Ulcers at 1, 3, & 6 months Trial PN400-301

	PN400-301 (n = 434)	
	Vimovo n = 218	Naproxen Control n=216
Ulcer Count Month 1 (%)	3 (1.38%)	29 (13.43%)
Ulcer Count Month 3 (%)	4 (1.83%)	41 (18.98%)
Ulcer Count Month 6 (%)	9 (4.13%)	50 (23.15%)

The observed incidence of gastric ulcers in the PP population was similar to the ITT population. Again treatment differences were seen as early as 1 month. The following figure provides a graphic look at the PP population. The incidence of gastric ulcers in the PP population for patients taking Vimovo was 1.5%, 2.0%, and 4.4% at 1, 3 and 6 months respectively. In the Naproxen group, the incidence of gastric ulcers among patients in the PP population was 13.9%, 20.4%, and 24.4% respectively at 1, 3 and 6 months.

Figure 2 Cumulative Observed Incidence of Gastric Ulcers at 1, 3 and 6 months PN400-301 Per Protocol Population (Percentages Reported)



A variety of studies have demonstrated with a fair amount of consistency, risk factors for NSAID-associated GI-toxicity. These risk factors include patient age (currently >65 years), chronic debilitating disorders (especially cardiovascular disease), high dose NSAID therapy, concurrent medications (e.g. low-dose aspirin), prior medical history of ulcer and Helicobacter Pylori infection.

The protective effect of Vimovo at reducing the incidence of gastric ulcers was maintained when the analysis accounted for low-dose aspirin use in the study population. At 1 month, none of the 53 patients taking Vimovo and low-dose Aspirin developed a gastric ulcer compared to 11.8% (6 of 51) of those taking Naproxen and low-dose Aspirin. This trend was maintained throughout the study. At 6 months, 1.9% of patients in the Vimovo + Low Dose Aspirin group developed a gastric ulcer compared with 23.5% of patients in the Naproxen + Low Dose Aspirin Group.

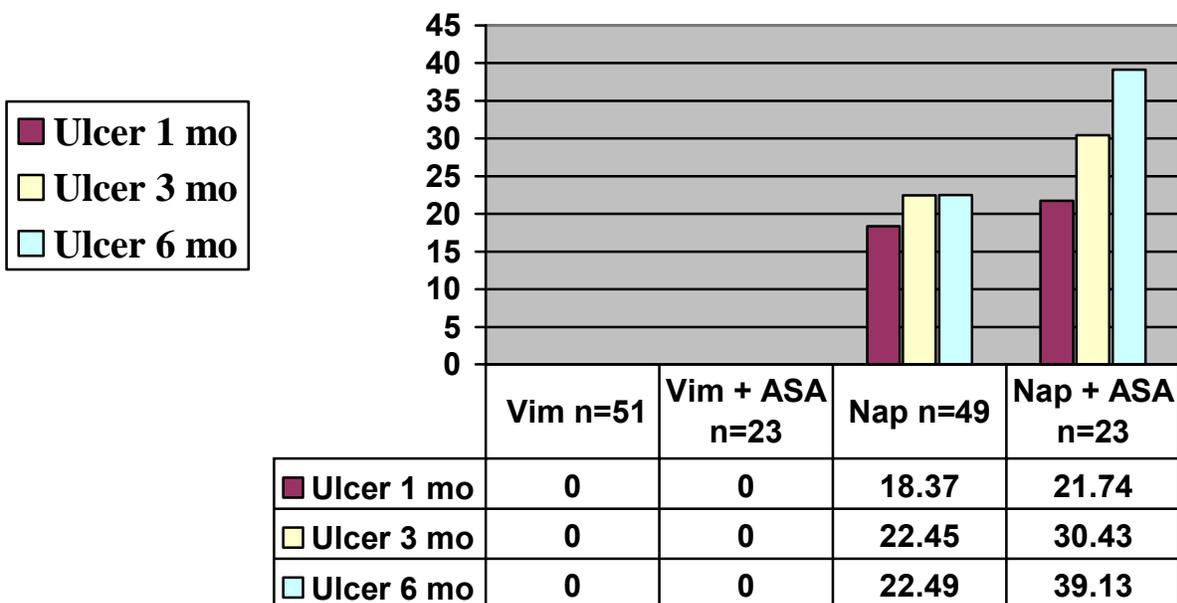
Additional results of the exploratory analysis of gastric ulcer incidence testing for the effect of baseline risk factors favored Vimovo. Conditional logistic regression analysis showed that those patients with a history of ulcer within the previous 5 years were 3.4 times more likely to develop an ulcer while taking the Vimovo relative to the Naproxen. There was no significant effect of age (>60 years or <60 years) on ulcer formation between the two groups in this trial.

Of note, the sponsor performed an exploratory efficacy analysis for patients over the age of 50 who had low dose aspirin use. In this analysis 3.1% of patients in the Vimovo group compared with 29.0% of patients in the Naproxen group developed a gastric ulcer at 6 months. The sponsor examined the incidence of gastric ulcers in those patients that

were over and under the age of 60. In patients who were over the age of 60 (232 patients), the cumulative observed incidence of gastric ulcers at 6 months was 0.9% (1/113) for the Vimovo group and 25.2% (30/119) for the Naproxen group.

The medical officer performed her own analysis and looked at patients over the age of 65 who also had concomitant low dose aspirin use at baseline. By 2009 guidelines published in the American Journal of Gastroenterology, this represents a high risk population for NSAID related ulcer complications.¹¹ Overall there were more ulcers at 6 months in the Naproxen control group relative to the Vimovo group in this sub analysis. However, this is only exploratory because the study was not powered to detect such a difference. The results of the medical officers exploratory sub analysis are presented in the graphic below

Figure 3 Cumulative Incidence of Patients Developing Gastric Ulcers in Participants \geq 65 years old with and without Low-Dose Aspirin Use PN400-301



Patients in the Vimovo group had a longer mean duration of exposure to study drug (159.6 days) than patients in the Naproxen group (120.3 days). The sponsor postulated that this could be attributed to the fact that considerably more patients completed 6 months of treatment and had no gastric ulcers in the Vimovo group (78%) compared to the Naproxen group (48%). The medical officer concurs. It also explains why the mean number of doses was higher for the Vimovo group (310.1 doses) relative to the Naproxen (225.7). The average doses per month was similar between the 2 treatment groups (58.5 doses of Vimovo and 57 doses of Naproxen) reflecting the common bid regimen of both groups.

The safety analysis was performed on all patients in the ITT population who received at least one dose of study drug. Per the sponsor, there were a total of 18 protocol violations in this trial (9 from the Vimovo and 9 from the Naproxen group). All the violations in the Vimovo group were patients who failed to get a post-baseline endoscopy done. In the Naproxen group, 3 patients failed to take the study drug and the remaining 6 failed to have a post-baseline endoscopy done. All of these patients plus those that did not have at least 70% compliance with study medication were excluded from the per-protocol population. Case report forms for 7 of these patients were submitted with the study report. Three reported worsening heartburn. One reported severe diarrhea. One had documented worsening hypertension. The other two had antral erosions.

The following table (reproduced from the sponsor’s submission) provides an overview of adverse events in the safety population. This data was confirmed by the medical reviewer.

Table 10 Overview of Adverse Events Safety Population Trial PN400-301

	Vimovo (N=218)	Naproxen (N=216)
Deaths	0	0
Study participants with at least 1 SAE	5 (2.3%)	6 (2.8%)
Discontinuations due to adverse events	14(6.4%)	24 (11.1%)
Study participants with at least 1 treatment-emergent adverse events	170 (78.0%)	176 (81.5%)
Study participants with at least 1 treatment-RELATED adverse events	108 (49.5%)	141 (65.3%)

Reviewer’s Table

There were no deaths reported in this study.

A total of twelve nonfatal serious adverse events were reported from 5 study participants in the Vimovo arm and 6 patients in the Naproxen arm. One patient (PN400-301-506-1177 was responsible for 2 nonfatal SAEs.) CRFs were reviewed for these study participants and the following table summarizes the medical officer’s findings.

There were a total of 3 SAEs under the SOC of cardiac disorders. Two of those were experienced by one patient in the Vimovo group (patient PN400-301506-1177). The other SAE was experienced by one patient from the Naproxen group (patient PN400-301-589-1758). None of the SAEs were felt to be related to the study drug and upon review of the narratives and CRFs, the medical officer concurs. Two patients (patient PN400-301-589-1642 from the Naproxen arm and patient PN400-301-589-1508 from the Vimovo arm) reported non-cardiac chest pain. Interestingly both reports of non-

cardiac chest pain were reported at site 589. The SAE reported from patient PN400-301-589-1642 occurred within the window of four weeks post-treatment.

Table 11 Serious Adverse Events for Trial PN400-301

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
PN400-301-490-1165	Vimovo	Musculoskeletal Pain	80yo white, Hispanic female, nonsmoker. Past medical history significant for hypertension, hypercholesterolemia, epigastric pain, heartburn, internal hemorrhoids, hematochezia, gastritis of the fundus and antrum, hiatal hernia, constipation, Type 2 diabetes, osteoarthritis, right shoulder dislocation and right rotator cuff tear. Patient is s/p cholecystectomy and complete hysterectomy. Patient had been taking Lisinopril, Lasix, Lantus and Lovastatin at the time of study entry. This patient experienced right shoulder pain that was significant enough to be classified as an SAE because it required hospitalization for pain control. During the hospitalization, use of study drug was interrupted and the patient was started on Vicodin and Nexium in addition to her regular medications. Eventually this patient was lost to follow-up and she did not complete the final study visit.	Unrelated
PN400-301-479-1166	Naproxen	Post-procedural Infection	51yo white, non-Hispanic, female, nonsmoker. Past medical history significant for hypertension, sinusitis, seasonal allergies, asthma, nonspecific chest pain, irritable bowel syndrome, osteoarthritis, recurring headaches, depression, heartburn, duodenitis, insomnia, and low back pain. Patient is status post multiple surgeries including bilateral knee arthroscopy, bilateral carpal tunnel surgery and cholecystectomy. Regular medications included Metoprolol, Captopril, Hydrochlorothiazide, Lexapro, Zyrtec, Advair, and Melatonin. During the trial, this patient tore her right meniscus and had an arthroscopic procedure done on her right knee. She subsequently developed an infection post-op. Pt was given Levaquin, Ancef, Vicodin, Skelaxin, and Lortab post-op. Study drug	Unrelated

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
			was discontinued and the patient was eventually withdrawn from the study. Final study visit completed.	
PN400-301-509-1424	Vimovo	Osteoarthritis	82 year old white, non-Hispanic, male, nonsmoker. Past medical history significant for short term memory loss, bilateral hearing loss, pacemaker, hypertension, hypercholesterolemia, nonspecific ST-T wave changes on screening EKG, osteoarthritis, right hip replacement, melanoma of lower back, nonerosive gastritis, abdominal hernia, urinary frequency. Pts regular medications included a baby aspirin, Metoprolol, Valsartan, Simvastatin, Aricept, and OTC Centrum A-Z. During the study the patient developed worsening osteoarthritis and pain in the left hip (significant enough to be classified as an SAE) for which he was given Celebrex. Patient completed final study visit.	Unrelated
PN400-301-513-1494	Naproxen	Diverticulitis	58 year old white, non-Hispanic, female, nonsmoker. Past medical history significant for poor vision, Hepatitis A, hypertension, diverticulitis, osteoarthritis, back pain, hiatal hernia, mild esophagitis. Patient is status post hysterectomy. Her regular medications included tenormin hydrochlorothiazide, Multivitamin, and Vitamin E. During the study, the patient experienced a diverticulitis flare that lasted 17 days. Study drug was discontinued at this time. Patient was started on IV Metronidazole tid, IV hydromorphone prn, promethazine prn, morphine prn during her hospitalization. She was given one dose of Rocephin and eventually was discharged on PO Bactrim and Promethazine. This patient was able to complete the final study visit.	Unrelated

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
PN400-301-589-1508	Vimovo	Non-cardiac Chest Pain	59 year old white, non-Hispanic female, nonsmoker. Past medical history includes anorexia, depression, post traumatic stress disorder, hypertension, heart murmur, erosive esophagitis, osteoarthritis, neuropathy of lower back and bilateral legs, degenerative disc disease, fibula fracture, tibia fracture, gallstones, pancreatitis, colon polyps, ovarian cysts, tonsillitis, cervical carcinoma insitu, myopia, hypercholesterolemia, Type II Diabetes, and pneumonia. Patient is status post laminectomy, hysterectomy, ovarian cyst removal and nerve stimulator placement. Her usual pain medications included a number of opioids and Mobic. Other regular medications included Metformin, Mirtazapine, Atorvastatin, Gabapentin, Vitamins E and B12, and Zolpidem Tartrate. Patient experienced nonspecific noncardiac chest pain which resolved on the same day it presented and did not require any rescue medications. During the patients hospitalization, cardiac enzymes were normal; an echo revealed symmetrical left ventricular hypertrophy with an EF of 62% and indications of diastolic dysfunction. Patient also underwent a stress EKG which was normal. Study drug was discontinued and the patient was withdrawn from the study. The patient did not complete a final visit.	Unrelated
PN400-301-479-1534	Vimovo	Ischemic Colitis	50 year old white Hispanic female nonsmoker. Past medical history significant for seasonal allergies, sinusitis, heartburn, gastric ulcers recurrent headaches, anemia, low back pain, uterine fibroids. Patient is status post tubal ligation and appendectomy. Regular medications included Claritin and Multivitamins. The SAE the patient experienced was a severe case of ischemic colitis lasting for two days and felt to be unrelated to the study drug. However during this time study drug was discontinued and the patient withdrawn from	Unrelated

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
			the trial. The final visit was completed.	
PN400-301-589-1642	Naproxen	Non-cardiac Chest Pain	84 year old white non-Hispanic male smoker. Past medical history includes seasonal allergies, recurrent bronchospasm, emphysema/COPD, hypertension, left ventricular hypertrophy, chest pain, lower leg claudication, hypothyroid, hypercholesterolemia, colonic polyps, guaic positive stools, recurrent urinary tract infection, increased PSA, positional vertigo, obstructive neuralgia, low back pain, hyperglycemia, bilateral knee osteoarthritis, cervical osteoarthritis, cervical fusion, lumbar disk herniation, degenerative joint disease bilateral knees, transient thrombocytopenia, recurrent tonsillitis, anxiety, insomnia, situational depression. Patient is status post tonsillectomy, appendectomy, right inguinal hernia repair. ECG findings were significant for a right bundle branch block and left anterior fascicular block. During the trial, patient developed nonspecific noncardiac related chest pain lasting one day. The investigators felt this was almost certainly related to the study drug. However, no rescue medications were required and the pain resolved. Patient was eventually withdrawn from the study after he developed a gastric ulcer. He did complete the final study visit.	Related
PN400-301-584-1655	Naproxen	Clostridium Difficile Colitis	64 year old white, non-Hispanic male nonsmoker. Past medical history includes rheumatoid arthritis, degenerative joint disease, atherosclerotic heart disease, tachycardia, hypertension, hyperlipidemia, fatty liver, atypical chest pain, palpitations, peripheral neuropathy, hiatal hernia, erosive esophagitis, gastritis, umbilical hernia, sleep apnea, and benign prostatic hypertrophy. Patients prior medications include atorvastatin, finasteride, metoprolol, glucosamine chondroitin, ocuvite, multivitamin, aspirin.	Unrelated

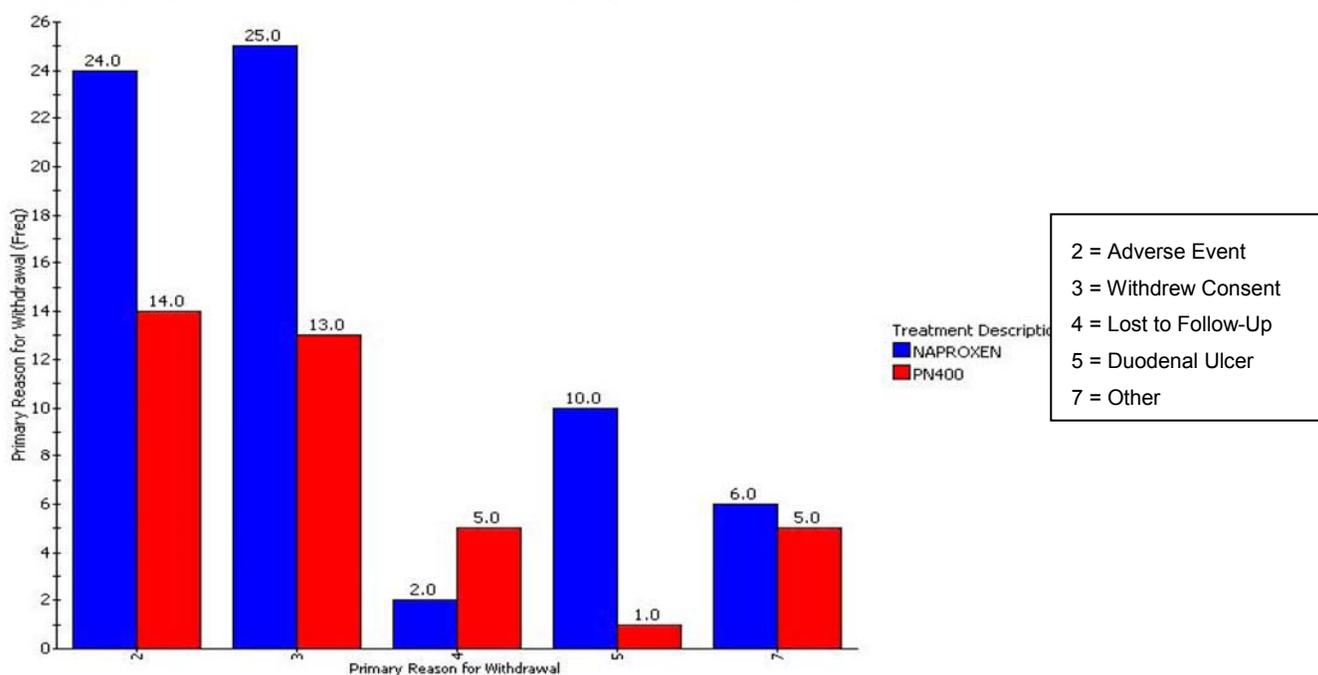
Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
			Patient developed clostridium difficile colitis requiring hospitalization for 3 days. This was felt to be unrelated to the study drug and patient continued on study medication. Pt did complete the final study visit.	
PN400-301-589-1758	Naproxen	Coronary Artery Disease	59 year old white, non-Hispanic female nonsmoker. Past medical history included presbyopia, hypertension, external hemorrhoids, constipation, post-menopausal syndrome and estrogen deficiency, osteoarthritis, osteopenia, heart burn, "fluttering in chest", fibrocystic breast changes, sleep disturbance, patellofemoral syndrome, situational depression, and insomnia and gastric polyps. Regular medications include fish oil, multivitamins, metoprolol, aspirin, simvastatin, clopidogrel, furosemide, potassium, darifenacin. This patient had no history of coronary artery disease. A baseline study EKG showed normal sinus rhythm, high QRS voltage and nonspecific anterolateral T wave abnormalities. The patient experienced chest tightness beginning in March 2008, approximately one month, after starting the study This was thought to be possibly related to the study drug but no action was taken. Coronary angiography was performed on April 22 which demonstrated coronary artery disease. This was felt to be unrelated to the study drug by the investigator. However, study drug was discontinued. The patient was withdrawn from the trial but did complete the final study visit.	Unrelated
PN400-301-608-1763	Naproxen		87year old white male nonsmoker. Past medical history included carpal tunnel syndrome, osteoarthritis, arthritic spurs, Hepatitis A, squamous cell carcinoma, basal cell carcinoma prostate cancer, bilateral hernias, bilateral cataracts. left leg edema, antral erosions, erosive esophagitis, problems with sleep. Patient is status post	Related

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
			<p>resection of carcinomas, prostate cancer radiation, bilateral hernia repair, and bilateral cataract removal. Regular medications included a multivitamin, vitamins C and D, selenium, temazepan, acetaminophen, and pantoprazole. Patient was eventually withdrawn from the study when he developed a bleeding duodenal ulcer and anemia. The investigators felt this was almost certainly related to the study drug and interrupted study drug therapy. Patient did complete the final visit.</p>	
<p>PN400-301-506-1177</p>	<p>Vimovo</p>	<p>Angina Unstable Myocardial Infarction</p>	<p>67 year old white, non-Hispanic, white female nonsmoker. Past medical history includes chronic obstructive pulmonary disease, seasonal allergies, hypothyroidism, irritable bowel syndrome, colon polyps, bladder incontinence and recurrent urinary tract infections, osteoporosis, degenerative joint disease, osteoarthritis, hemorrhoids, hiatal hernia, breast cancer, diverticulosis, palpitations, hypertension, coronary artery disease, duodenal ulcer, antral erosions, GERD. Patient is status post mastectomy, right hip replacement and cholecystectomy. Patients medications included atenolol, enablex, multivitamins, vitamins E & C, allegra, advair, vesicare, allopurinol, nasal bactroban, aspirin, astelin spray, imdur, synthroid, norvasc. Study baseline EKG revealed normal sinus rhythm with some ST abnormalities. This patient experienced 2 SAEs. (The first, unstable angina, was reported March 2008. The second, a peri-operative MI, was reported late in June 2008) Patient was hospitalized for unstable angina. On initial evaluation patient reported a two month history of chest pain that worsened over the past 1 to 2 weeks. During her workup the patient underwent coronary angiography which revealed 4 vessel disease. Pt was</p>	<p>Unrelated</p>

Patient Number	Treatment	MedDRA Preferred term for SAE	Narrative	Relatedness
			transferred to another facility for coronary bypass surgery. She subsequently experienced a peri-operative myocardial infarction and post-operative ventricular tachycardia. Study drug was interrupted due to this event. The patient was withdrawn from the study and did not complete the final study visit.	

The figure below provides a graphic look at the primary reason for withdrawal by treatment group.

Figure 4 Study PN400-301 Primary Reason for Withdrawals by Treatment



Most of the patients that withdrew from the study were from the Naproxen Group. There were 14 patients from the Vimovo arm and 24 patients from the Naproxen arm that withdrew because of an adverse event. The majority of the AEs leading to discontinuation (9 in the Vimovo arm and 17 from the Naproxen arm) were from the Gastrointestinal Disorders SOC. There were 2 AEs in the Cardiac SOC that lead to discontinuation (1 in each of the treatment arms: patients PN400-301-589-1758 and PN400-301-506-1177). Both of the Cardiac AEs do not appear to be related to the study drug. Only one patient (PN400-301-490-1499) discontinued the study due to a mild elevation in blood creatinine that was possibly related to study drug. The patient was in the Vimovo group. The event was ongoing at the time the study participant terminated the study.

Five patients in the Vimovo arm were lost to follow up. Two patients in the Naproxen group were lost to follow-up.

The overall adverse event rate was fairly comparable between the Naproxen group (82%) relative to the Vimovo group (78%). The percentage of study participants reporting an adverse event did not appear to vary significantly with treatment exposure.

Treatment related adverse events were reported for 50% of study participants in the Vimovo treatment group and 65% of study participants in the Naproxen group. The most frequently reported treatment related adverse events were from the GI SOC and included the preferred terms erosive gastritis, gastritis, and dyspepsia. The majority of events were mild or moderate. In the Vimovo group, 9.2% experienced a severe adverse event as opposed to 13.9% of the Naproxen. The majority of the severe adverse events were from the GI SOC and dyspepsia appeared to be the most frequently reported event in both treatment groups. Clinically dyspepsia is a very broad term that can include a number of symptoms but it usually refers to pain in the upper or middle abdomen. Rome III criteria for functional dyspepsia is defined as at least 3 months, with onset at least 6 months previously of 1 or more of the following: bothersome post-prandial fullness, early satiation, epigastric pain, epigastric burning AND no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

5.3.3 Clinical Overview of Trial PN400-302

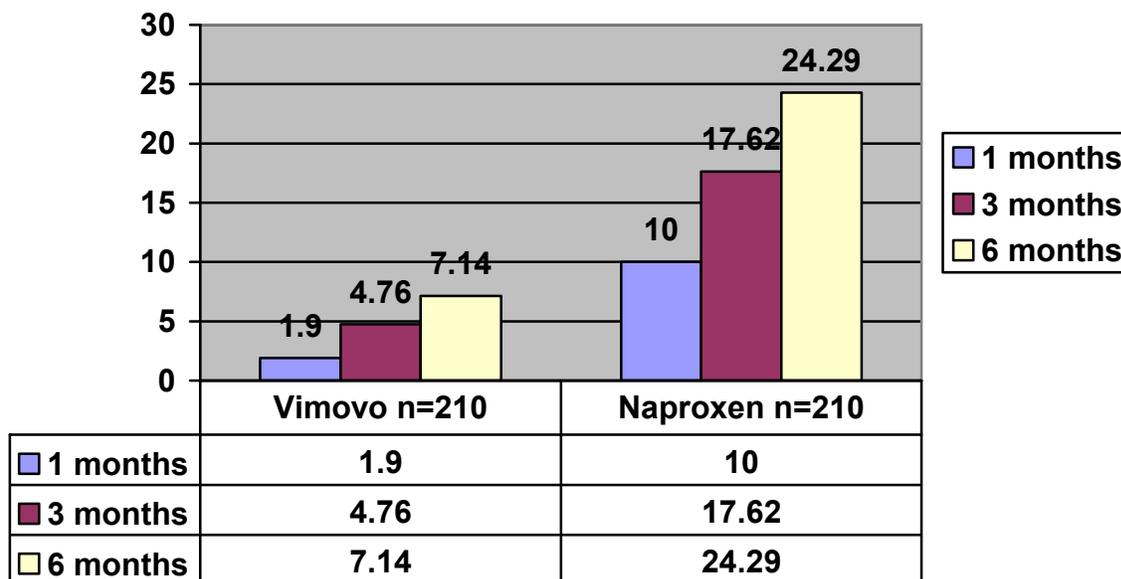
See Section 6 below for additional information. There were 210 patients in Vimovo and Naproxen arms respectively in this study. Summaries of baseline demographics below are based on the ITT population. Baseline characteristics for both treatment arms of the study were similar. For both groups, the population was predominantly White (87 – 91%), Non-Hispanic (68 – 82%), and female (68 – 63%). The proportion of Latinos to Non-Latinos was higher in the control arm than in the Vimovo arm. The mean age was 59.6 years in the Vimovo arm and 59.4 years in the Naproxen arm. When patients were stratified for low-dose aspirin use, 21.9% of the Vimovo group consisted of low-dose aspirin users compared with 24.3% of the Naproxen group. There was an imbalance in the patients with a history of gastric ulcers. In the Vimovo arm, 5.7% of patients had a history of gastric ulcer whereas 10% of patients in the Naproxen arm had a history of gastric ulcer. The percentage of patients having a history of a duodenal ulcer was similar between the two arms (2.9% for Vimovo and 2.4% for Naproxen). Overall when you look at the patients with a history of ulcer within the previous 5 years, there was less of a discrepancy (8.6% in the Vimovo arm and 11.0% in the Naproxen arm).

Table 12 Baseline Demographics Trial PN400-302 (ITT Population)

Characteristic	PN400-302 (n = 420)	
	Vimovo	Control
Age (years):		
Mean (std)	59.6 (8.2%)	59.4 (8.3%)
Median	59	58
Min, Max	27, 85	29,82
Age Group:		
< 60	111 (52.9%)	120 (57.1%)
<50	8 (3.8%)	6 (2.9%)
50-59	103 (49.0%)	114 (54.3%)
≥ 60	99 (47.1%)	90 (42.9%)
Sex		
Male	78 (37.1%)	68 (32.4%)
Female	132 (62.9%)	142 (67.6%)
Race		
White	183 (87.1%)	190 (90.5%)
Black	26 (12.4%)	17 (8.1%)
Asian	1 (0.5%)	2 (1.0%)
Ethnicity		
Hispanic/Latino	38 (18.1%)	68 (32.4%)
Not Hispanic or Latino	172 (81.9%)	142 (67.6%)

All efficacy analyses were performed using the intent-to-treat (ITT) and per-protocol populations (PP). Following the intent-to-treat principle, study participants were analyzed according to the treatment group they were assigned to at randomization. The primary efficacy endpoint was the proportion of study participants developing gastric ulcers throughout the 6 months of treatment. Overall the cumulative observed incidence of gastric ulcers was lower in the Vimovo group (7.14% vs. 24.29%) relative to the Naproxen group. A significant difference was seen as early as 1 month. The figure below provides a graphic presentation of the data.

Figure 5 Cumulative Observed Incidence of Patients Developing Gastric Ulcers at 1, 3, and 6 months Trial PN400-302 ITT population (Percentages Reported)



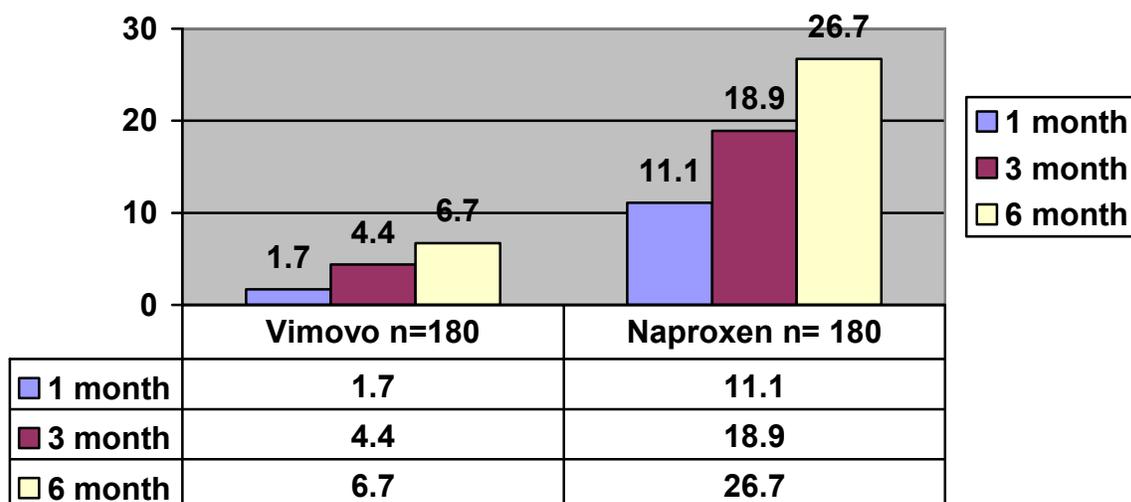
At 1 month, 1.9% of those in the Vimovo group developed a gastric ulcer as opposed to 10% in the Naproxen group. At 6 months, 7.14% of the Vimovo group developed a gastric ulcer, whereas 24.29% of the Naproxen group developed a gastric ulcer.

Table 13 Cumulative Incidence of Patients Developing Gastric Ulcers at 1, 3, & 6 months Trial PN400-302

	PN400-302 (n = 420)	
	Vimovo n = 210	Naproxen Control n = 210
Ulcer Count Month 1 (%)	4 (1.90%)	21 (10.00%)
Ulcer Count Month 3 (%)	10 (4.76%)	37 (17.62%)
Ulcer Count Month 6 (%)	15 (7.14%)	51 (24.29%)

The results of the observed incidence of gastric ulcers in the per-protocol population were similar to the ITT population. Again treatment differences were seen at 1 month. The figure below shows the results of the analysis of cumulative observed incidence of gastric ulcers.

Figure 6 Cumulative Observed Incidence of Patients Developing Gastric Ulcers at 1, 3, and 6 months PN400-302 PP Population (Percentages reported)



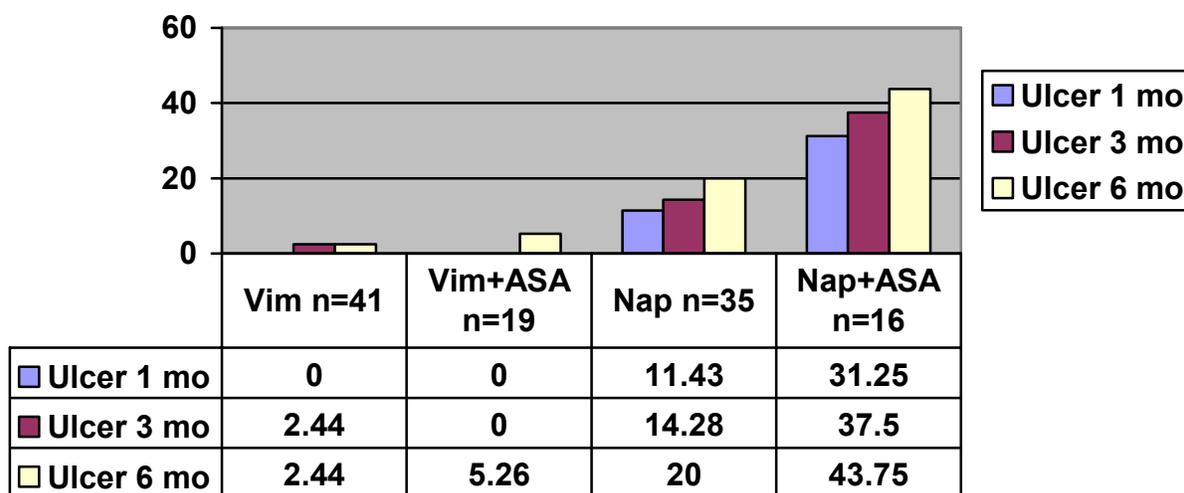
The effect of Vimovo at reducing the incidence of gastric ulcers was maintained when the analysis accounted for low-dose aspirin use in the trial population. At 1 month, none of the patients taking both Vimovo and low-dose aspirin developed a gastric ulcer. However, 19.61% of the patients taking Naproxen and low-dose aspirin developed a gastric ulcer. By the end of 6 months, 4.34% of patients on Vimovo and low-dose aspirin developed a gastric ulcer. In contrast, 33.33 percent of those taking Naproxen and low-dose aspirin developed a gastric ulcer.

Results of the exploratory analysis of gastric ulcer incidence while taking into account the effect of baseline risk factors favored Vimovo. Vimovo's effects did not seem to be altered by race or gender. In those patients that have a previous history of ulcer, 1.43% in the Vimovo group and 4.29% in the Naproxen group developed an ulcer at the end of 6 months.

The sponsor also performed an exploratory analysis of the efficacy endpoint in patients who were over and under the age of 60 years. For those patients over the age of 60 years, 5.1% in the Vimovo arm developed a gastric ulcer whereas 27.8% in the Naproxen arm developed a gastric ulcer at the end of 6 months. Again the medical officer performed her own analysis on patients who were over the age of 65 years with

and without low-dose aspirin use. By current American Gastroenterology Association Guidelines this is a high risk population. The results are provided in the graphic below. Again this is an exploratory analysis only.

Figure 7 Cumulative Incidence of Patients Developing Gastric Ulcers in Trial Participants who are ≥ 65 years old with and without Low Dose Aspirin Use PN400-302 (Reported in Percentages)



Study participants in the Vimovo group had a longer mean duration of exposure (144.1 days) than patients in the Naproxen group (127.9 days). The mean number of doses was also higher in the Vimovo group (280.5 doses) relative to the Naproxen group (244.6 doses). This would be consistent with an anticipated higher drop out rate due to ulcers in the Naproxen group. The average doses per month were similar between the two treatment groups (mean was 56.6 for Vimovo and 56.8 for Naproxen).

The safety analysis was performed on all patients in the ITT population who received at least one dose of study drug. There were a total of 28 major protocol violations (12 in the Vimovo group and 16 in the Naproxen group). All of these violations were study participants with no post-baseline endoscopy. Three of the study participants also did not take study drug. The Per-Protocol population excluded 30 patients from each treatment group of the ITT population. Those excluded were those with major protocol violations and those with study drug compliance <70%.

The following table (reproduced from the sponsor's submission) provides an overview of adverse events in the safety population. These numbers were confirmed by the medical officer.

Table 14 Overview of Adverse Events Safety Population Trial PN400-302

	Vimovo (N=210)	Naproxen (N=216)
Deaths	0	0
Study participants with at least 1 SAE	5 (2.4%)	7 (3.3%)
Discontinuations due to adverse events	20 (9.5%)	30 (14.3%)
Study participants with at least 1 treatment-emergent adverse event	160(76.2%)	174 (82.9%)
Study participants with at least 1 treatment-related adverse event	109 (51.9%)	143 (68.1%)

Reviewer's Table

There were no deaths in this trial.

Twelve patients experienced 13 SAEs. Five of these study participants were in the Vimovo group and 7 were in the Naproxen group. One patient (patient 489-2471) experienced two nonfatal SAEs. Case Report Forms and narratives were reviewed for each of these study participants and the following table summarizes the medical officer's findings. There were no SAEs related to the study drug.

Table 15 Serious Adverse Events for Trial PN400-302

Patient Number	Treatment	Preferred Term for SAE	Narrative	Relatedness
PN400-302-0418-2282	Vimovo	Suicide Attempt	51yo Black, non-Hispanic Male smoker. Past medical history significant for GERD and Osteoarthritis in the knees. Patient was not on any medications prior to starting the study. The SAE was a suicide attempt that required hospitalization for further work-up. . The patient did not complete a final visit and was lost to follow-up.	Unrelated
PN400-302-0478-2210	Naproxen	Diabetic Ulcer	59yo White non-Hispanic Male Smoker. Past medical history of recurrent pharyngitis, blurred vision, hypertension, occasional nausea, peripheral edema in the legs and feet, non-insulin dependent diabetes mellitus, osteoarthritis, right wrist, right ankle and left elbow fracture, inguinal hernia, ?Raynaud's, obesity, psoriasis, COPD, peripheral vascular disease and deep vein thrombosis. Prior medications include metformin, lisinopril, glyburide, quinidine sulfate, novolog, proventil, atrovent. The patient experienced a blunt trauma to his left lower extremity one month prior to study site visit. At that visit, physical exam revealed severe left lower extremity ulcers and the patient was hospitalized for evaluation and treatment. Arterial dopplers showed possible occlusion of the left iliac artery. It is unclear from the narrative what additional vascular work-up or intervention was done. The patient's wounds were treated and he was released home on antibiotics with wound care.	Unrelated
PN400-302-0478-2285	Naproxen	Concussion	55yo White, non-Hispanic Male Smoker. Past medical history significant for heartburn, nausea, Mallory-Weiss tears, renal lithiasis, recurrent muscle spasms, osteoarthritis, degenerative joint disease, low-back pain, depression, anxiety, and panic attacks. Patient is status post lithotripsy and laser stone	Unrelated

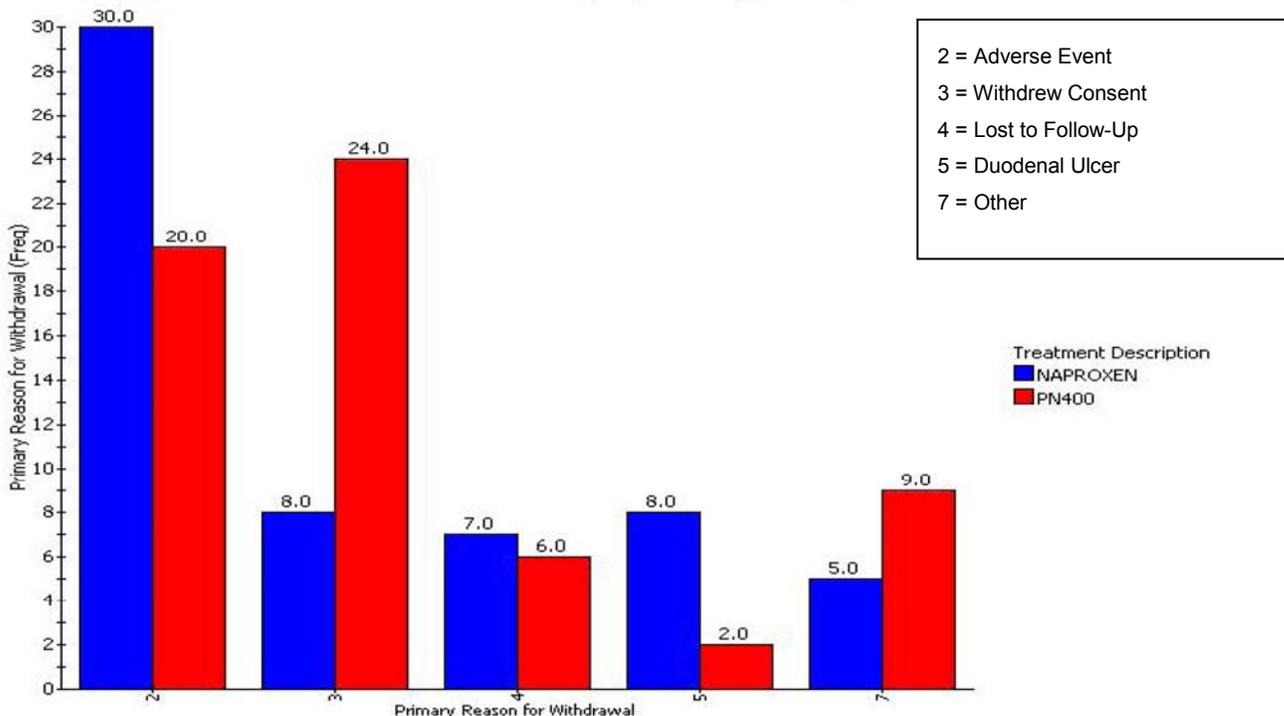
Patient Number	Treatment	Preferred Term for SAE	Narrative	Relatedness
			removal. Prior medications included flexeril, ativan, paxil, temazepam, lortab, habitrol, toradol, and protonix. The patient fell and incurred a head laceration and abrasions to his arms and legs. This required 3 day hospitalization for treatment, care and evaluation. There was no evidence of hemorrhage, mass or fracture during the work-up. Study drug was interrupted during this time. The patient did complete the final study visit.	
PN400-302-0489-2471	Naproxen	Pneumonia Urinary Tract Infection	53 year old Black, non-Hispanic female, nonsmoker. Past medical history included hyperlipidemia and degenerative joint disease. Patient is status post hyperectomy and right knee surgery. Her usual medications included Vytorin and Aspirin. On May 8, patient developed Bronchitis and study drug was discontinued. Patient subsequently developed progressive shortness of breath, fever, chills, and a productive cough. She was hospitalized and treated for pneumonia. During her initial evaluation, urinalysis also revealed an E.Coli urinary tract infection. Both the pneumonia and UTI were treated with Levaquin. The patient was also given Xopenex and Atrovent. The patient did complete the final study visit.	Unrelated
PN400-302-0489-2568	Vimovo	Syncope	59 year old White, non-Hispanic male nonsmoker. Past medical history included obesity, hyperlipidemia, coronary artery disease, hypertension, angina, non-insulin dependent diabetes mellitus, sleep apnea, gastric ulcer, diverticulosis, degenerative joint disease, hemorrhoids, and restless leg syndrome. Prior medications included metformin, allopurinol, vytorin, lisinopril, aspirin, flomax, zyrtec, nexium and zantac. Patient was hospitalized for a syncopal episode. Work-up including EKG, Head CT, and Chest CT were negative. Symptoms were attributable to laryngeal spasm secondary to reflux and the	Unrelated

Patient Number	Treatment	Preferred Term for SAE	Narrative	Relatedness
			patient was discharged from the hospital. Study medication was discontinued and the patient completed the final study visit.	
PN400-302-0502-2053	Naproxen	Chronic Obstructive Pulmonary Disease	80 year old White, Non-Hispanic male nonsmoker. Past medical history included seasonal allergies, myopia, hypertension, coronary artery disease, dyslipidemia, GERD, benign prostatic hypertrophy, depression, anxiety, degenerative joint disease, low-back pain, myalgia, chronic obstructive pulmonary disease, congestive heart failure. Prior medications included diltiazem, simvastatin, enalapril, flomax, lexapro, lortab, diazepam, temazepam, diltiazem, albuterol, pepcid, flomax, celexa, proscar, lasix, potassium, nexium, lexapro, atrovent, Benadryl, novolog insulin, and various antibiotics. The patient is status post CABG and carotid end arterectomy. The patient experienced an exacerbation of his COPD resulting in hospitalization in the ICU approximately 5 months after randomization into the study. The patient was treated with antibiotics and high dose steroids as well as diuretics. Additional hospital events included the diagnosis of steroid-induced hyperglycemia and urinary tract infection. Study medication was interrupted during this event. The patient did complete the final visit.	Unrelated
PN400-302-0502-2055	Vimovo	Atrial Fibrillation	64 year old White, non-Hispanic, male smoker. Past medical history included chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, Type II diabetes, hypertension, nonerosive gastritis and duodenitis, low back pain and erectile dysfunction. Patient was status post coronary stent placement. Patient was found to have a complete left bundle branch block on screening EKG. Prior medications included Spiriva, Chantix, Cardizem, Lasix, Mucomyst, Advair, Tikosyn,	Unrelated.

Patient Number	Treatment	Preferred Term for SAE	Narrative	Relatedness
			Coreg, Amiodarone, Digoxin, Dofetilide, The patient experienced atrial flutter resulting in hospitalization. After failure to convert using pharmacotherapy, patient underwent external DC conversion to sinus rhythm. Study medication was discontinued in response to the SAE.	
PN400-302-0525-2044	Vimovo	Mastectomy	73 year old white, non-Hispanic female nonsmoker. Past medical history significant for hypertension, gastric ulcer, diverticular disease, tension headaches, osteoarthritis, rheumatoid arthritis, transient ischemic attack, spinal stenosis, osteoporosis, memory loss, insomnia and depression. During the treatment phase of the trial, patient had a screening mammogram which revealed a mass that was found to be malignant on biopsy. Study drug was discontinued and the patient dropped from the trial. The patient did not complete the final study visit.	Unrelated
PN400-302-0573-2531	Naproxen	Upper Limb Fracture	57 year old White, non-Hispanic female nonsmoker. Past medical history significant for GERD and osteoarthritis. Patients regular medications included melatonin. Patient experienced a fall and landed on an outstretched right arm. In the ER, she was diagnosed with a fracture of the distal radius. She was hospitalized for repair and pain management. Study medication was discontinued in response to this event. Patient did complete the final study visit.	Unrelated
PN400-302-0590-2624	Naproxen	Palpitations (Adrenal mass)	55 year old White, non-Hispanic male, nonsmoker. Patient has a history of allergic rhinitis, asthma, hypertension, mitral valve prolapse, hyperglycemia, osteoarthritis, hyperlipidemia, and sleep apnea. Prior medications included metoprolol, allegra-D, zyrtec, rhinocort, maxzide, hydrochlorothiazide, prilosec, avelox, mucinex. The patient was hospitalized after presenting to the	Unrelated

Patient Number	Treatment	Preferred Term for SAE	Narrative	Relatedness
			ER with intermittent palpitations and chest pain. Work-up was negative and the patient was discharged 2 days after initial hospitalization. Study drug was discontinued at this time. Of note, approximately 2 weeks later the patient again presented to the ER. This time complaining of abdominal pain. An abdominal CT revealed a left adrenal mass.	
PN400-302-0590-2625	Naproxen	Fracture	65 year old White, non-Hispanic male nonsmoker. Past medical history significant for hearing loss, chronic obstructive pulmonary disease, GERD, BPH, alzheimers, degenerative disc disease, osteoarthritis, incomplete bundle branch block. The patient was involved in a roll-over motor vehicle accident and suffered fractures of his cervical vertebrae. No additional information was available for this patient. The patient did not complete the final study visit.	Unrelated
PN400-302-0590-2396	Vimovo	Post-procedural hemorrhage	68 year old White, non-Hispanic, female nonsmoker. Past medical history included hypertension, hyperlipidemia, hypothyroidism, urinary frequency, osteoarthritis, rheumatoid arthritis, depression, seasonal allergies, osteopenia, osteoporosis, GERD. Medications included Zetia, Simvastatin, Neurontin, Levothyroid, Fluoxetine, Triamterene hydrochlorothiazide. This patient underwent colonoscopy and polypectomy 2 days before randomization into the trial. Three days after randomization the patient was hospitalized after presenting to the ER with rectal bleeding while stooling. Work-up was negative except for diverticulosis of the sigmoid colon. Patient received 3 units of packed red blood cells and was discharged on hospital day #4. After the SAE resolved, the patient continued in the study and completed 6 months of treatment.	Unrelated

Figure 8 Primary Reason for Withdrawal Trial PN400-302



More study participants withdrew because of an adverse event in the Naproxen arm (30 patients) relative to the Vimovo arm (20 patients). The majority adverse events leading to discontinuation were from the Gastrointestinal disorders SOC. The most common adverse events leading to study discontinuation was upper abdominal pain and erosive gastritis. Most of the adverse events leading to study discontinuation were moderate in severity. All study participants who had SAEs were withdrawn from the study with the exception of patient PN400-302-0478-2285 and patient PN400-302-0590-2624. Both patients were in the Naproxen group. Patient PN400-302-0478-2285 experienced a concussion secondary to a fall. Study drug was interrupted but was resumed after work-up and treatment. Patient PN400-302-0590-2623 was off study drug for 8 days prior to onset of the symptoms. More patients in the Naproxen arm developed AEs leading to discontinuation (14.3%) than those in the Vimovo arm (9.5%)

Interestingly more patients in the Vimovo arm withdrew consent or stopped the trial because of “other” reasons. Because the medical reviewer noticed a large number of study participants withdrew consent, an information request was sent to the sponsor to provide a summary of the reasons the 24 patients in the Vimovo arm withdrew consent. A sampling of the case report forms for these patients was also requested. The following is a summary of reasons for withdrawal of consent.

Figure 9 Summary of Reasons for Withdrawal of Consent Trial PN400-302

Number of Study Participants	Reason	Study Participant Number
5	Lack of Efficacy	2007, 2155, 2229, 2553, 2714
7	Did not want to undergo multiple endoscopies	2047, 2106, 2199, 2457, 2532, 2588, 2699
2	Relocated	2501, 2679
1	Work schedule conflict	2379
1	Distance to travel too far	2672
1	Not able to comply with study procedures	2213
1	Did not want to continue in the study	2175
1	Failure to show for scheduled appointment	2591
1	Wanted to participate in another study	2075
1	Could not meet time requirements of study	2656
1	Concerned regarding comment made about another physician at study site	2530
1	Amount of pills to take was too great	2444
1	Starting anti-rejection medications for preexisting condition	2080

The overall rate of treatment emergent adverse events reported by study participants was comparable between the Naproxen group (82.9%) and the Vimovo group (76.2%). Treatment-related adverse events were reported for 52% of study participants in the Vimovo group and 68% in the Naproxen group. Overall, treatment-related GI adverse events occurred less often with Vimovo (48.6%) than with Naproxen (65.7%). Like PN400-301, the most frequently reported treatment related adverse events were erosive gastritis (17.1% for Vimovo; 37.1% for Naproxen) and dyspepsia (16.7% for Vimovo; 22.9% for Naproxen). The adverse event rate increased with exposure time in both treatment groups. However, the overall treatment-related AE rate was less in the Vimovo group (51.9%) relative to the Naproxen group (68.1%)

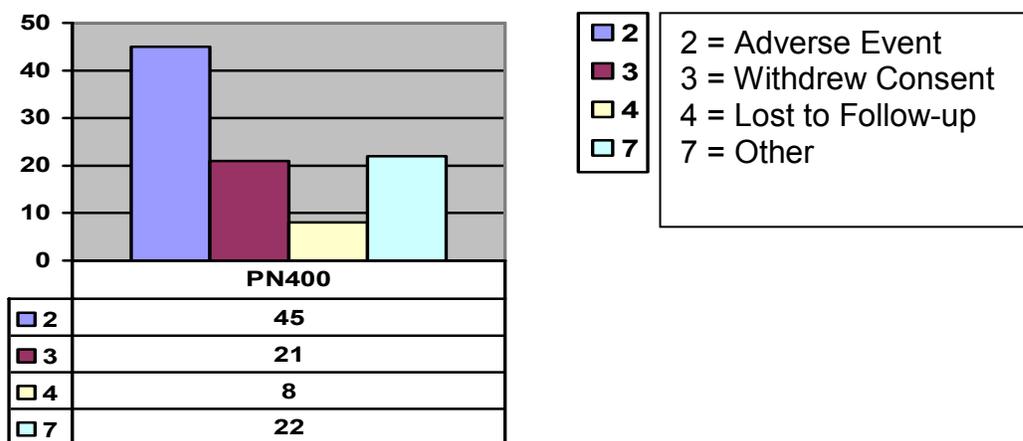
5.3.4 Clinical Overview of Trial PN400-304

The majority of patients in the long term safety trial were white (88.3%), female (70.3%), non-Hispanic (82.4%), and nonsmokers (87.4%). The mean age was 60.8 years. Approximately half of the patients enrolled in the study were over the age of 60. The majority of patients (69%) were not low-dose aspirin users. However, most (58.6%) had a history of an upper gastrointestinal disorder or some form of cardiovascular history (59.4%). The most common concomitant medications used by study participants were the lipid modifying agents.

The safety population consisted of the 239 study participants enrolled in the trial. The mean duration of exposure was 270.7 days in the overall all safety population. The mean duration of exposure was 359.3 days in those patients that completed 12 months of the study. (Twelve month completers were defined as taking study medication for at least 348 days. Of the 239 enrolled study participants, 135 (57%) were considered to be 12-month completers.) All of the study participants in the twelve-month population were compliant with study medication. The high withdrawal rate is somewhat concerning given that this is the population that most likely will reflect the adverse events in those using the drugs chronically.

The primary reasons for withdrawal from the trial are depicted in the graphic below.

Figure 10 Primary Reason for Withdrawal Trial PN400-304



In the long-term safety study (PN400-304), of the 239 study participants who enrolled, 96 individuals (40%) discontinued from the study prematurely. Forty five (19%) withdrew due to an adverse event. Twenty one (9%) of study participants withdrew consent.

With the exception of ulcer formation, there were no trends towards an increased frequency of discontinuations with the longer duration of therapy or increased exposure.

An overview of the adverse events that occurred during this trial are outlined in the table below.

Table 16 Overview of Adverse Events Trial PN400-304

	Safety Population N=239	12-Month Completers N=135
Deaths	0	0
Study participants with at least 1 SAE	13 (5.4%)	1 (0.7%)
Discontinuations due to adverse events	45 (18.8%)	1 (0.7%)
Study participants with at least 1 treatment-emergent adverse event	175 (73.2%)	95 (70.4%)
Study participants with at least 1 treatment-RELATED adverse event	67 (28.0%)	32 (23.7%)

Reviewer's Table created using Sponsor's Combined ADSL and ADAE datasets submitted for Trial PN400-304.

There were no deaths during the long-term safety study. Thirteen of the study participants in the safety population experienced at least 1 SAE. Pneumonia was the only SAE that occurred twice (patients PN400-304-506-4074 and PN400-404-397-4217).

Two study participants experienced 2 SAEs. Patient PN400-304-537-4229 experienced both mental confusion and acute non-cardiac chest pain on the same day. These were reported as separate AEs. Study medication was discontinued in response to the events. The medical officer does not believe that either of these SAEs are related to the study drug. Details are provided in the table below. Patient PN400-304-519-4132 was initially withdrawn from the study after experiencing a transient ischemic attack. However this patient had a complicated medical history and it is impossible to determine if the TIA was the result of study drug use or the patient's other comorbidities. This patient subsequently underwent a right carotid endarterectomy. Three weeks later the patient experienced an episode of atrial fibrillation. Neither of the SAEs in this patient appears to be related to the study drug.

Patient PN400-304-537-4193 was withdrawn from the study after experiencing a transient ischemic attack. However it is unlikely that this was related to the study drug, as the patient had a number of other comorbid conditions that could have contributed to the TIA. Likewise patient PN400-304-478-4110 also experienced a TIA that was most like the result of underlying coronary artery disease.

Three of the SAEs appear to be possibly related to the study drug. Patient PN400-304-478-4056 experienced an episode of hematemesis requiring hospitalization. An upper

gastrointestinal endoscopy revealed hemorrhagic gastritis. Study medication was discontinued and the incident resolved. Patient PN400-304-478-4110 experienced worsening of back pain and patient PN400-304-398-4177 experienced worsening left knee pain.

The following table provides an overview of the SAEs in this trial

Table 17 Serious Adverse Events for Trial PN400-304

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
PN400-304-506-4074	Vimovo	Pneumonia	70 year old White, NonHispanic, Male Nonsmoker. Past medical history included hypertension, hyperlipidemia, diabetes, diabetic peripheral neuropathy, osteoarthritis, gastroesophageal reflux, overactive bladder, diverticulosis, colon polyps, anxiety and insomnia. Medications included metformin, lisinopril, lyrica, flomax, and ambien. Patient initially presented to ED with a history of dyspnea, fever, fatigue, and a productive cough. Although the patient was afebrile on presentation with a negative chest xray, he was hospitalized and treated with IV azithromycin (and subsequently oral azithromycin). Three days after being discharged from the hospital, the patient was withdrawn from the study due to increase heartburn.	Unrelated
PN400-304-478-4056	Vimovo	Hematemesis	62 year old White, NonHispanic, Male, Nonsmoker. Past medical history includes Type II diabetes, hypercholesterolemia, hypertension, peripheral vascular disease, arrhythmia, anxiety, depression, multiple eye problems, GERD, gastroparesis, osteoarthritis of the knees (s/p multiple knee surgeries) and Parkinsons disease. Medications included simvastatin, insulin, glipizide, glyburide, metformin, lisinopril, zofran, gabapentin, phenytoin, entacapone and carbidopa-levodopa. Two days prior to hospital admission, the patient experienced stomach discomfort and nausea. He reported numerous episodes of vomiting and reported some blood-tinged emesis on the day of presentation to the ED. Gastric	Possibly

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			aspirate obtained via NG tube was positive for blood The patient was treated with IV pantoprazole. Patient underwent upper endoscopy which revealed areas of hemorrhagic gastritis but no active bleeding. The patient was also noted to have an elevated blood pressure which was treated with labetalol, enalapril, and hydralazine without improvement. BP was eventually controlled with IV nitroprusside. Serum creatinine was slightly elevated on admission but returned to normal during the hospital course. Additional workup (which included a head CT scan and renal ultrasound) was negative. The patient was discharged 1 week after initial hospital admission with a primary diagnosis of hematemesis and secondary diagnosis of hypertensive crisis. The medical officer does believe that these events were possibly related to study drug but no definitive conclusions can be made.	
PN400-304-500-4032	Vimovo	(Staphylococcus Infection Reported by Investigator) Chest Pain as assessed by the reviewer	55 year old White, NonHispanic, female nonsmoker. Past medical history included hypertension, hypertension, hypercholesterolemia, gastric ulcer, GERD, chronic constipation, gallstones (s/p cholecystectomy), nephrolithiasis, lumbar back pain, depression, Previous medications included zoloft, zocor, lisinopril, zofran, nitroglycerin. The patient was admitted to the hospital for cardiac evaluation chest pain, diaphoresis, dyspnea, and tingling of the left arm. The patient underwent cardiac catheterization which revealed no evidence of coronary artery disease and normal LVF. The patient also had a negative V/Q scan and lower extremity ultrasound for	(Unrelated per Investigator) Possibly

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			<p>thrombophlebitis. No other details were available on the hospital course. The patient was discharged from the hospital 4 days after admission. Approximately 1 week after discharge, the patient again presented to the ED complaining of right-sided upper abdominal pain, radiating to her back and associated with nausea. Patient was hospitalized and an abdominal CR revealed a nodular structure in the biliary hilum. An endoscopic ultrasound and fine needle aspiration of the mass was performed. Fluid from the mass was positive for staphylococcus on culture. It was believed that the mass was secondary to the patient's prior cholecystectomy. The patient was discharged and recovered with Levaquin. The investigator believed the two hospitalizations were related to each other and unrelated to study drug. H The medical officer believes that a more conservative approach should have been taken and the events should have been reported separately as chest pain and infection. The chest pain possibly may have been related to the study drug. However the staph infection was unrelated to the study drug.</p>	
PN400-304-489-4086	Vimovo	Coronary Artery Disease	<p>54 year old Black, NonHispanic, Female Smoker. Past medical history included hypertension, type II diabetes, hyperlipidemia, gastritis, gastroparesis, colon polyps, chronic back pain, degenerative disc disease, chronic constipation, restless legs, palpitations, pericarditis. Prior medications included glucophage, lantus, actos, cozaar, triamterene, hydrochlorothiazide, lipitor, aspirin, plavix,</p>	Possibly

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			<p>diovan, The patient developed chest pain radiating to the jaw and left arm pain lasting for about 15 minutes. Patient was transported to ED where cardiology suggested a cardiac catheterization. The patient was transferred again and underwent left heart catheterization with coronary angiography that revealed coronary artery disease. Patient underwent percutaneous angioplasty and stenting of the right coronary artery and was subsequently discharged 3 days after initial presentation. One week after discharge the patient experienced recurrent chest pain and presented again to the ED for evaluation. Repeat catheterization with angiography demonstrated a patent right coronary artery with normal LVF and the patient was discharged from the hospital.</p>	
<p>PN400-304-509-4189</p>	<p>Vimovo</p>	<p>Complete heart Block</p>	<p>76 year old Black, NonHispanic, Male Nonsmoker. Past medical history significant for hypertension, osteoarthritis, arrhythmia, erosive esophagitis, schatzki's ring, right bundle branch block, bifascicular block, bradycardia, syncope, cutaneous herpes. Medications include a baby aspirin, valsartan, nifedipine, hydrochlorothiazide, lysine, nifedipine. The patient presented to an outpatient clinic reporting confusion and difficulty staying alert. Physical exam demonstrated a heart rate of 32bpm with a blood pressure of 120/50. EKG revealed a complete heart block. The patient was transferred and admitted to the hospital. Upon arrival the patient was alert, oriented, denying chest pain, abdominal pain, and dyspnea. Repeat EKG demonstrated a complete heart block with idioventricular</p>	<p>Unrelated</p>

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			<p>escape rhythm of 26 beats per minute. Doppler echocardiogram demonstrated normal LVF with normal ejection fraction, thickening of the mitral and aortic valves, mild mitral and tricuspid regurgitation and pulmonary hypertension. Acute myocardial infarction was ruled out by cardiac enzymes. Patient underwent placement of a dual chamber sequential pacemaker on the day of admission. The patient was discharged the following day with complete resolution of the event.</p>	
<p>PN400-304-492-4095</p>	<p>Vimovo</p>	<p>Necrotic fasciitis</p>	<p>68 year old White, NonHispanic Female Nonsmoker. Past medical history includes osteoarthritis, hypertension, hypercholesterolemia, asthma, seasonal allergies, gastritis, and hemorrhoids. Patient is status post total hysterectomy, appendectomy, and repair of fractured left ankle. Medications included losartan, atorvastatin, aspirin, albuterol, allegra, fluticasone, amlodipine, glucosamine, chondroitin. The narrative presented is somewhat confusing because it states that the patient stopped taking study medication on (b) (6) after developing flu-like symptoms 2 days prior. However, this would have occurred during the time the patient was hospitalized. Reportedly the patient was hospitalized on (b) (6) for treatment of a perianal abscess with necrotizing fasciitis. The patient was treated with cephalexin and metronidazole after the affected area was excised, debrided, and drained. The patient was discharged on hospital day #21 (b) (6) with complete resolution by (b) (6). Notwithstanding, the sequence of events, it is very unlikely that the event</p>	<p>Unrelated.</p>

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			was related to study.	
PN400-304-537-4193	Vimovo	Transient Ischemic Attack	57 year old White, NonHispanic, female Nonsmoker. Past medical history included obesity, osteoarthritis, diabetes, hypertension, hypothyroidism, migraines, gastritis, colonic polyps, seasonal allergies, depression and panic attacks. Previous medications included skelaxin, nortriptyline, metformin, allegra, reglan, paroxetine, triamterene hydrochlorothiazide, amlodipine, synthroid, rhinocort, OTC vitamins. The patient was admitted to the hospital after presenting to the ER with a left facial droop and hemiparesis of the left upper and lower extremity associated with a headache. The patient also reported mild posterior neck pain. Head CT was negative for structural abnormalities. Lab testing revealed a high glucose and cholesterol levels and normal cardiac enzymes. Urine culture was positive for E.coli. The patient was treated with low dose aspirin, atorvastatin and antibiotics. During the hospitalization, the patient's neurological function recovered and the patient was discharged the day after admission.	Unlikely
PN400-304-397-4217	Vimovo	Pneumonia	85 year old White, Hispanic, male nonsmoker. Past medical history included glaucoma, asthma, emphysema, osteoarthritis, hypertension, hyperlipidemia, occasional rhinitis, cataracts, skin melanomas and renal cell carcinoma (s/p nephrectomy), Medications included albuterol, atrovent, pulmicort, lovastatin, diovan, and aspirin. Patient was hospitalized following a 2 day history dyspnea and productive cough. A chest xray did not reveal	Unrelated

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			active pulmonary infiltrates, however oxygen saturation was 92%. White blood cell count was 21,000 cells/cm ³ The patient was discharged after 4 days of hospitalization on levofloxacin, atrovent and albuterol nebulizers and a prednisone taper.	
PN400-304-519-4132	Vimovo	Carotid Artery Stenosis And Atrial Fibrillation	76 year old white, nonHispanic, male, nonsmoker. Past medical history included morbid obesity, hyperlipidemia, hypertension, COPD, glaucoma, gallstones, benign prostatic hypertrophy, chronic back pain. Medications included aspirin, simvastatin, timolol, triamterene, hydrochlorothiazide, and lisinopril. The patient experienced sudden loss of vision in both eyes accompanied by limb paralysis. A limited amount of vision returned after 1 hour. The following morning the patient had largely returned to normal but sought medical attention. A carotid ultrasound revealed greater than 80% occlusion of the left internal carotid artery and 40-59% occlusion of the right internal carotid. The patient underwent right carotid endarterectomy 22 days later and was discharged the following day. The patient was discontinued from the study after the endarterectomy was performed. When the patient reported for his study termination visit, he reported feeling dizzy and sweaty. An EKG done on site revealed atrial fibrillation with a rapid ventricular response. The patient was transported to the hospital ED for further evaluation and treatment. Repeat EKG showed atrial fibrillation with a ventricular rate of 114 beats/minute and non-specific ST-T wave changes. The	Unrelated.

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			<p>patient was treated with IV diltiazem and SQ enoxaparin. Following initial therapy the event resolved with the patient converting to a sinus rhythm during hospital day #1. Cardiac consult diagnosed the patient with paroxysmal atrial fibrillation secondary to hypertensive cardiomyopathy with recent endarterectomy as a possible contributing factor. The patient was discharged on hospital Day #2 on metoprolol.</p>	
PN400-304-398-4151	Vimovo	Thyroid Cancer	<p>54 year old White NonHispanic male smoker. Past medical history significant for hypertension, hyperlipidemia, GERD, osteoarthritis, depression and multimodal goiter. Patient is s/p multiple surgeries. Medications included Enalapril, Actos, Metoprolol, Zetia, Effexor, Lipitor, Humulin, Lantus, Byetta, Catapres, Calcitriol, Calcium plus Vitamin D. Per report, the patient experienced increasing difficulty related to the goiter and underwent a near total thyroidectomy. A small cuff of the thyroid gland was left with preservation of the superior laryngeal nerve. The final pathology report was consistent with multi-nodular hyperplasia and papillary carcinoma. A whole body scan was performed on the patient that demonstrated 2 areas of uptake localized to the thyroid. The patient underwent ablation therapy with radioactive iodine and the event resolved 3 months after initial onset.</p>	Unrelated
PN400-304-478-4110	Vimovo	Worsening back pain	<p>68 year old White NonHispanic male nonsmoker. Past medical history included obesity, diabetes, hyperlipidemia, hypertension, pitting edema lower extremities (possibly</p>	Possibly

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
			secondary to CHF), osteoarthritis, degenerative disc disease, spinal stenosis, spondylolisthesis, lumbar scoliosis, diverticulitis, benign prostatic hypertrophy, prior transient ischemic attack and a heart murmur. Medications included metformin, actos, aspirin, norvasc, zocor, hydrochlorothiazide, flomax, prinivil, januvia, simcor, aspirin. The patient experienced worsening low back pain and bilateral leg achiness and numbness. Few details are provided in the narrative. However, it appears the patient was hospitalized twice. The second time the patient underwent decompression lumbar laminectomy of L4-L5 and L5-S1 with decompression bilaterally of L4, L5, and S1; posterior spinal fusion of L4, L5, and S1 with right iliac crest autograft and demineralized bone matrix laminectomy.	
PN400-304-398-4177	Vimovo	Worsening Left Knee Pain	74 year old White, NonHispanic, male, nonsmoker. Past medical history included hypertension, hypothyroidism, sinus arrhythmia, osteoarthritis, heartburn, hiatal hernia, seasonal allergies. Medications included diltiazem and levothyroid. In (b) (6), the patient experienced worsening symptoms of this left knee osteoarthritis and was scheduled for elective total joint replacement. The procedure occurred 3 months later. The patient was discharged to a rehabilitation hospital for surgical recovery.	Possibly

Patient Number	Treatment	MedDRA Preferred Term for SAE	Narrative	Relatedness
PN400-304-537-4229	Vimovo	Mental Confusion And Non-cardiac chest pain	57 year old White, NonHispanic, male, nonsmoker. Past medical history included hypertension, hyperlipidemia, narcolepsy, osteoarthritis, gastritis, esophagitis, myopia, and overactive bladder. Patient is s/p orchiectomy for a right testicular cyst. Medications include atenolol, zetia, centrum silver, anafranil, hydrochlorothiazide, vesicare, provigil, zocor, The patient initially presented to the ED with a 1 day history episodes of mental confusion, unsteady gait, and chest pain. The chest pain was described as sharp with substernal and left-sided radiation. Further evaluation of the chest pain revealed normal cardiac enzymes, normal ECG, normal chest Xray, and normal chest CT. Neurology was consulted. During the hospitalization the patient continued to demonstrate an unsteady gait with a right-sided lean. Head CT, brain MRI, extracranial and intracranial MRA were normal. The patient was initially discharged the next day after his symptoms resolved.	Possibly.

Forty five patients discontinued the trial due to an adverse event. Gastrointestinal adverse events led to withdrawal of 19 (8%) of the trial participants. The most common adverse event leading to discontinuation was dyspepsia which occurred in six patients. Adverse events leading to study drug discontinuation in more than 1 patient are presented in the table below.

Table 18 Adverse Events Leading to Discontinuation in Trial PN400-304

System Organ Class/ Preferred Term	Vimovo Safety Population N = 239
Study Participants with at least 1 adverse event leading to discontinuation	45 (18.8%)
Gastrointestinal Disorders	19 (17.9%)
Dyspepsia	6 (2.5%)
Abdominal pain upper	2 (0.8%)
Constipation	2 (0.8%)
Gastroesophageal reflux disease	2 (0.8%)
Musculoskeletal and Connective Tissue Disorders	11 (4.6%)
Arthralgia	2 (0.8%)
Back pain	2 (0.8%)
Osteoarthritis	2 (0.8%)
General disorders and administration site conditions	3 (1.3%)
Peripheral edema	2 (0.8%)

The overall discontinuation rate due to adverse events did not seem vary with age. The overall discontinuation rate due to adverse events was 20% in the <60 year old group and 18% in the ≥60 year old group. The discontinuation rate also did not appear to increase over time.

For this drug class, we'd be most concerned about changes in hematological and liver function parameters when looking at the laboratory data. The majority of patients in the safety population did not experience any major changes in their hemoglobin, alkaline phosphatase, ALT, AST, or total bilirubin. Laboratory shifts from baseline are provided in the table below.

Table 19 Trial PN400-304 Laboratory Shifts from Baseline Using Expanded Laboratory Normal Range

	Overall Safety Population (N=239)	Twelve-Month Completers (N=135)
ALKALINE PHOSPHATASE (U/L)		
Low or Normal -> High	0	0
High or Normal -> Low	0	0
No Change	238 (100.0%)	135 (100.0%)
Change to Normal	0	0
Total	238	135
ALT (U/L)		
Low or Normal -> High	2 (0.8%)	1 (0.7%)
High or Normal -> Low	0	0
No Change	235 (98.7%)	134 (99.3%)
Change to Normal	1 (0.4%)	0
Total	238	135
AST (U/L)		
Low or Normal -> High	3 (1.3%)	2 (1.5%)
High or Normal -> Low	0	0
No Change	235 (98.7%)	133 (98.5%)
Change to Normal	0	0
Total	238	135
BILIRUBIN, TOTAL (mg/dL)		
Low or Normal -> High	0	0
High or Normal -> Low	0	0
No Change	238 (100.0%)	135 (100.0%)
Change to Normal	0	0
Total	238	135
BUN (mg/dL)		
Low or Normal -> High	0	0
High or Normal -> Low	0	0
No Change	238 (100.0%)	135 (100.0%)
Change to Normal	0	0
Total	238	135
CREATININE (mg/dL)		
Low or Normal -> High	3 (1.3%)	2 (1.5%)
High or Normal -> Low	0	0
No Change	235 (98.7%)	133 (98.5%)
Change to Normal	0	0
Total	238	135
GLUCOSE, RANDOM (mg/dL)		
Low or Normal -> High	10 (4.2%)	4 (3.0%)
High or Normal -> Low	0	0
No Change	223 (93.7%)	128 (94.8%)
Change to Normal	5 (2.1%)	3 (2.2%)
Total	238	135
MAGNESIUM (mEq/L)		
Low or Normal -> High	0	0
High or Normal -> Low	1 (0.4%)	0
No Change	237 (99.6%)	135 (100.0%)
Change to Normal	0	0
Total	238	135

| Sponsor's Table copied from Clinical Study Report PN400-304 p. 376/440

6 Review of Efficacy

Efficacy Summary

For this submission, the analgesic efficacy of Vimovo was based on bioequivalence of the Naproxen component to EC-naprosyn and demonstrated superiority of Vimovo to placebo in trials PN400-307 and PN400-309. (Studies PN400-307 and PN300-309 were reviewed by Dr. Jin Chen from the Division of Anesthesia, Analgesia, and Rheumatology Products separately).

The efficacy analysis for the risk reduction of ulcers was based upon data from Studies PN400-301 and PN400-302. Both trials were randomized, double blind, active controlled trials conducted over 6 months comparing Vimovo with EC-Naproxen. A total of 861 study participants were enrolled in the two pivotal trials. Seventy four percent (74%) of those enrolled, completed the trial. By the end of 6 months, 94.4% of patients taking Vimovo remained gastric ulcer free compared with 76.3% of patients taking Naproxen. This was statistically significant (p value <0.001). Based on the data that was provided, the two pivotal studies demonstrate that Vimovo does reduce the incidence of gastric ulcers in patients relative to enteric-coated Naproxen alone.

The sponsor wants to make the same claim for both the 375mg and 500mg dosage strengths of Vimovo. In terms of reducing the number of gastric ulcers, this seems acceptable because both forms contain the same amount of esomeprazole (20mg). One could deduce that if Vimovo tablets were successful in reducing the incidence of gastric ulcers with the higher 500mg Naproxen dose, it would also be successful in reducing the incidence of ulcer occurrence in the 375mg dose.

6.1 Indication

The sponsor seeks the following indication for Vimovo tablets:

- Relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in participants at risk for developing NSAID-associated gastric ulcers.

The medical officer can only provide a review of the information submitted in support of Vimovo's ability to reduce gastric ulcers. This clinical efficacy analysis will focus on the pivotal trials PN400-301 and PN400-302.

6.1.1 Methods

Please see section 5.3 above for more information. The five Phase III trials submitted with this application are summarized in table 4 above. Please note these tables also include information on the Phase I studies, reviewed by clinical pharmacology. The clinical efficacy of Vimovo for the proposed indication was evaluated in two 6 month, Phase III, randomized, double-blind, parallel group, active controlled multicenter trials (PN400-301 and PN400-302). Both studies were identically designed to demonstrate reductions in gastric ulcer occurrence over 6 months in patients taking Vimovo 500mg/20mg twice a day compared with those taking 500mg of Naproxen twice a day. (The details of these protocols can be found in Section 9.4).

The sponsor also submitted two 12 week randomized, double-blind supportive studies (PN400-307 and PN400-309) to assess the efficacy of Vimovo tablets against celecoxib and placebo for treatment of the signs and symptoms of patients with osteoarthritis of the knee. These were reviewed by DAARP, Dr. Jin Chen.

A 12 month open label long-term safety study (PN400-304) was conducted to evaluate the long-term safety of Vimovo in patients. (Details for this protocol can also be found in Section 9.4)

6.1.2 Demographics

Please also refer to section 5.3 and Section 7.21.

Both of the pivotal trials (PN400-301 and PN400-302), enrolled a majority of White, Non-Hispanic female patients. The mean and median ages were between 58 and 62 years. Per protocol, patients were considered at risk developing gastric ulcers if they were between the ages of 18 - 49 with a history of gastric ulcer or if they were over the age of 50 regardless of ulcer history. Consequently, the majority of patients enrolled were deemed at risk because of age greater than 50. This is the population that is more likely to have higher rates of cardiovascular disease and comorbid conditions. Less than 10% of the population had a previously documented history of ulcer in all of the trial arms, except for the Naproxen arm of Trial PN400-302. This may have implications if the sponsor attempts to make any extrapolations for ulcer complications in the labeling as a previous history of ulcer formation is a risk factor for developing a clinically significant ulcer related event. This higher number of patients with an ulcer history in the Naproxen group could theoretically exaggerate any differences in clinical outcomes between the two groups.

One approach for risk stratification of NSAID induced GI toxicity is outlined below:¹¹

- **High Risk**
 - History of a previously complicated ulcer, especially recent
 - Multiple (>2) risk factors

- **Moderate Risk (1-2 risk factors)**
 - Age >65 years
 - High dose NSAID therapy
 - A previous history of uncomplicated ulcer
 - Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants

- **Low Risk**
 - No Risk Factors

- H. Pylori is an independent and additive risk factor and needs to be addressed separately. Usually H. Pylori infection is associated with duodenal ulcers and is more prevalent in minorities and those from lower socio-economic classes.

Table 20 Baseline Demographic Distribution Across Pivotal Trials (ITT Populations)

Characteristic	PN400-301 (n = 434)		PN400-302 (n = 420)	
	Vimovo (n = 218)	Naproxen Control (n = 216)	Vimovo (n=210)	Naproxen Control (n=210)
Age (years):				
Mean (std)	60.8 (8.8)	61.9 (8.5)	59.6 (8.2%)	59.4 (8.3%)
Median	60.0	61.0	59	58
Min, Max	30, 90	43, 90	27, 85	29,82
Age Group:				
< 60 years	105 (48.2%)	97 (44.9%)	111 (52.9%)	120 (57.1%)
<50 years	6 (2.8%)	3 (1.4%)	8 (3.8%)	6 (2.9%)
50-59 years	99 (45.4%)	94 (43.5%)	103 (49.0%)	114 (54.3%)
≥ 60 years	113 (51.8%)	119 (55.1%)	99 (47.1%)	90 (42.9%)
Sex				
Male	68 (31.2%)	67 (31.0%)	78 (37.1%)	68 (32.4%)
Female	150 (68.8%)	149 (69.0%)	132 (62.9%)	142 (67.6%)
Race				
White	184 (84.4%)	181 (83.8%)	183 (87.1%)	190 (90.5%)
Black	27 (12.4%)	32 (14.8%)	26 (12.4%)	17 (8.1%)
Asian	4 (1.8%)	2 (0.9%)	1 (0.5%)	2 (1.0%)
Ethnicity				
Hispanic or Latino	45 (20.6%)	47 (21.8%)	38 (18.1%)	68 (32.4%)
Not Hispanic or Latino	173 (79.4%)	169 (78.2%)	172 (81.9%)	142 (67.6%)
Smoker				
Yes	32 (14.7%)	27 (12.5%)	36 (17.1)	38 (18.1%)
No	186 (85.3%)	189 (87.5%)	174 (82.9%)	172 (81.9%)
Documented History of Ulcer:				
Gastric	12 (5.5%)	10 (4.6%)	12 (5.7%)	21 (10.0%)
Duodenal	1 (0.5%)	0 (0.0%)	6 (2.9%)	5 (2.4%)
Both	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
None	204 (94.0%)	206 (95.4%)	192 (91.4%)	183 (87.1%)
Ulcer w/in previous 5 yr				
Yes	15 (6.9%)	13 (6.0%)	18 (8.6%)	23 (11.0%)
No	203 (93.1%)	203 (94.0%)	192 (91.4%)	187 (89.0%)

The sponsor also stratified for low-dose aspirin use at baseline. Approximately one quarter of patients in all both treatment arms of both studies were low dose aspirin users.

Table 21 Low-Dose Aspirin Use Pivotal Trials PN400-301 and PN400-302

	Vimovo	Naproxen
Trial PN400-301	N = 218	N = 216
Use Low-Dose Aspirin	53 (24.3%)	51 (23.6%)
No Low-Dose Aspirin Use	165 (75.7%)	165 (76.4%)
Trial PN400-302	N = 210	N = 210
Use Low-Dose Aspirin	46 (21.9%)	51 (24.3%)
No Low-Dose Aspirin Use	164 (78.1%)	159 (75.7%)

There were no measurements of efficacy in the open-label safety trial (PN400-304). The demographics and baseline characteristics of those enrollees were similar to that of the pivotal trials.

6.1.3 Subject Disposition

Table 22 Accountability and Disposition of Trial Enrollees Trial PN400-301 and PN400-302

	PN 400			EC Naproxen			Total
	301	302	Total	301	302	Total	
Randomized, N	218	212	430	220	211	431	861
Treated (Safety Population)	218 (100%)	210 (99.1%)	428 (99.5%)	216 (98.2%)	210 (99.5%)	426 (98.8%)	854 (99.2%)
ITT Population	218 (100%)	210 (99.1%)	428 (99.5%)	216 (98.2%)	210 (99.5%)	426 (98.8%)	854 (99.2%)
PP Population	203 (93.1%)	180 (84.9%)	383 (89.1%)	201 (91.4%)	180 (85.3%)	381 (88.4%)	764 (88.7%)
Completed study	180 (82.6%)	151 (71.2%)	331 (77.0%)	153 (69.5%)	153 (72.5%)	306 (71.0%)	637 (74.0%)
Completed study without gastric ulcer	171 (78.4%)	136 (64.2%)	307 (71.4%)	103 (46.8%)	102 (48.3%)	205 (47.6%)	512 (59.5%)
Prematurely Discontinued	38 (17.4%)	61 (28.8%)	99 (23.0%)	67 (30.5%)	58 (27.5%)	125 (29.0%)	224 (26.0%)
Adverse event	14 (6.4%)	20 (9.4%)	34 (7.9%)	24 (10.9%)	30 (14.2%)	54 (12.5%)	88 (10.2%)
Withdrew consent	13 (6.0%)	24 (11.3%)	37 (8.6%)	25 (11.4%)	8 (3.8%)	33 (7.7%)	70 (8.1%)
Lost to follow-up	5 (2.3%)	6 (2.8%)	11 (2.6%)	2 (0.9%)	7 (3.3%)	9 (2.1%)	20 (2.3%)
Duodenal ulcer	1 (0.5%)	2 (0.9%)	3 (0.7%)	10 (4.5%)	8 (3.8%)	18 (4.2%)	21 (2.4%)
Other	5 (2.3%)	9 (4.2%)	14 (3.3%)	6 (2.7%)	5 (2.4%)	11 (2.6%)	25 (2.9%)

Statistical Reviewers Table

Of the 861 patients randomized in the pivotal studies, 637(74%) completed the study. Disposition of enrollees is shown in the table above.

Per the sponsor the Intent-to-treat (ITT) population was defined as all randomized subjects who received at least one dose of study drug and had no ulcer detected by endoscopy at the Screening Visit. The safety population was defined as all randomized subjects who received at least one dose of study drug. The Per-protocol (PP) population was defined as all subjects in the ITT population who did not violate the protocol in any major way that would have impacted the evaluation of efficacy and had at least 70% overall treatment compliance. The sponsor claimed that subjects excluded from the PP

population were identified prior to unblinding of the treatment code, and the reason for exclusion was documented. Overall almost 89% of those patients randomized were also included in the per-protocol population. Overall, the PP population contained a similar number of total patients being treated with Vimovo (383) and Naproxen (381). However, more patients were excluded from the PP population in PN400-302 than PN400-301.

Overall, the percentage of patients taking Naproxen and completing the study was noticeably less (71% vs. 77%) than those taken Vimovo. This was because of a substantially larger percentage of patients taking Naproxen (30.5%) dropping out in trial PN400-301 relative to Vimovo (17.4%). Roughly equal numbers of both treatment arms completed trial PN400-302 (71.2% for Vimovo vs. 72.5% for Naproxen). See the table above. Per protocol patients found to have endoscopic ulcers were to be dropped from the trial. Assuming that Vimovo was more effective at reducing the occurrence of ulcers, it seems reasonable that more patients would drop out in the Naproxen group. This is consistent with what we see in PN400-301 but does not seem consistent with the dropout rate of PN400-302.

The sponsor stated that withdrawal of consent accounted for the majority of premature discontinuation from the EC Naproxen group in PN400-301 (25 subjects, 11% of those randomized). Withdrawal of consent also accounted for the majority of premature discontinuations in PN400-302. Overall more study participants treated with EC Naproxen withdrew from the pivotal studies than those treated with Vimovo for reasons other than protocol required withdrawal for endoscopic ally discovered gastric ulcers. Statistically, if these cases are labeled as treatment failures during analysis, it has the potential to show that Vimovo is more effective than it truly is.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable is the incidence of gastric ulcers at anytime throughout 6 months of treatment. An ulcer was defined as a mucosal break of at least 3mm in diameter (measured by close application of open endoscopic biopsy forceps) with depth. The primary efficacy endpoint was the proportions of subjects developing gastric ulcers throughout six months of study treatment. The cumulative proportion of study participants developing gastric ulcers at six months was analyzed using a Cochran-Mantel-Haenszel test stratified by low-dose aspirin use at randomization.

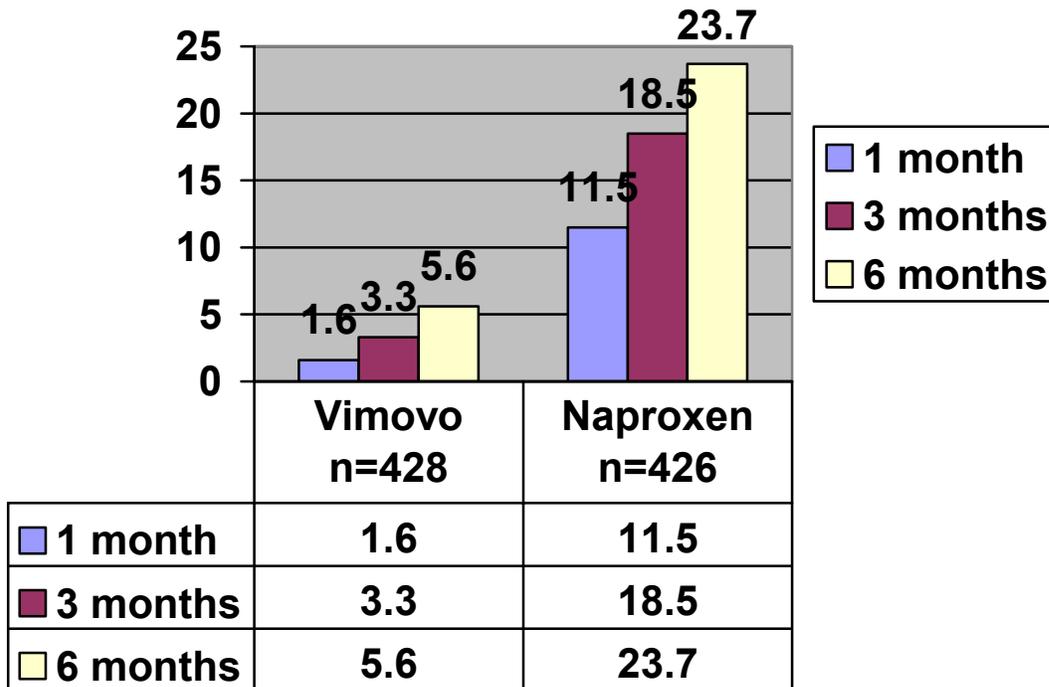
Is the primary endpoint chosen by the sponsor clinically meaningful? Distinguishing between an ulcer and an erosion can be difficult for the less experienced endoscopists. It is not without limitations. Most endoscopically diagnosed ulcers are asymptomatic. However, the definition of an ulcer used in the current trial as an endpoint has been used previously in GI trials for drugs seeking the indication of the risk reduction of ulcers. The sponsor stated that gastric ulcers are clinically important and also represent biomarkers for more serious upper GI clinical outcomes such as bleeding, perforation,

and obstruction. At present, data on the use of endoscopic ulcers as a surrogate marker for clinical outcomes is limited, however, there appears to be a positive association present.

The medical reviewer performed a literature review of the definition of ulcers used in clinical trials. A review of the literature was also conducted to determine the relationship between ulcer formation and clinical outcomes. One metaanalysis reviewing 45 publications, found that in 25 publications an ulcer was defined using a diameter of \geq 3mm with depth.¹² The medical reviewer was unable to find any studies assessing the relationship between the risk of developing ulcer-related complications and ulcer diameter. However, it is reasonable to assume that any true ulcer (an excavation that penetrates thru the muscularis mucosa into the submucosa) regardless of size may carry some risk of complication even if the severity of the complication can not be predicted.

The outcome results of the individual clinical trials are outlined above in Sections 5.3.1 and 5.3.2. Overall there were significantly fewer patients taking Vimovo who developed a gastric ulcer than those taking enteric coated Naproxen in both trials PN400-301 and PN400-302 (p-value <0.001). An effect was seen as early as 1 month. By 6 months, 94.4% of patients taking Vimovo remained gastric ulcer free compared with 76.3% of patients taking Naproxen.

Figure 11 Analysis of Cumulative Observed Incidence of Patients Developing Gastric Ulcers (in Percentages) at 1, 3, and 6 months (ITT Population from Combined Trials PN400-301 and PN400-302)



The following table provides data for the graphic depicted above. This data is consistent with the outputs generated by the statistical reviewer.

Table 23 Analysis of Cumulative Observed Incidence of Patients Developing Gastric Ulcers at 1, 3, and 6 months Intent to Treat Population Trials PN400-301 and PN400-302

	Vimovo (n = 428)	Naproxen (n = 426)
0 – 1 Month		
Gastric Ulcer 95% Confidence Interval	7 (1.6%) (0.7% - 3.3%)	49 (11.5%) (8.6% - 14.9%)
Gastric Ulcer-Free	421 (98.4%)	377 (88.5%)
Maintained Gastric-Ulcer Free	378 (88.3%)	320 (75.1%)
Discontinued Gastric Ulcer-Free	43 (10.0%)	57 (13.4%)
0 – 3 Months		
Gastric Ulcer 95% Confidence Interval	14 (3.3%) (1.8% - 5.4%)	79 (18.5%) (15.0% - 22.6%)
Gastric Ulcer-Free	414 (96.7%)	347 (81.5%)
Maintained Gastric-Ulcer Free	331 (77.3%)	247 (58.0%)
Discontinued Gastric Ulcer-Free	83 (19.4%)	100 (23.5%)
0 – 6 Months		
Gastric Ulcer 95% Confidence Interval	24 (5.6%) (3.6% - 8.2%)	101 (23.7%) (19.7% - 28.0%)
Gastric Ulcer-Free	404 (94.4%)	325 (76.3%)
Maintained Gastric-Ulcer Free	307 (71.7%)	205 (48.1%)
Discontinued Gastric Ulcer-Free	97 (22.7%)	120 (28.2%)

Reviewer's Table Adapted from Table E1.7 p147/372 Sponsor's Integrated Summary of Efficacy

Per the statistical reviewer, more data was missing from the Naproxen group in PN400-301. This data was imputed as treatment failures which resulted in a more favorable outcome for Vimovo. However, missing data from PN400-302 was more balanced between the treatment groups and similar outcome results were obtained. Sensitivity analysis performed by both the sponsor and the statistical reviewer did not reveal any inconsistency of the primary analysis results.

6.1.5 Analysis of Secondary Endpoints(s)

The sponsor also proposed to use data from the ITT population for analysis and treatment comparisons of the secondary efficacy and tolerability variables.

The key secondary efficacy variable was the incidence of duodenal ulcers at any time during the 6 months of treatment. (Note: The same definition of ulcer applied for the secondary efficacy variable.)

Key secondary tolerability variables included:

- The proportion of participants with pre-specified NSAID-associated UGI AEs or duodenal ulcers.
- The proportion of participants discontinuing the study due to NSAID-associated UGI AEs or due to duodenal ulcers

The choice of secondary endpoints seems appropriate. Ulceration may occur anywhere along the gastrointestinal tract. Chronic NSAID use can result in duodenal ulcers, although usually to a lesser extent than gastric ulcers. Duodenal ulcers are usually associated with H. Pylori infection. However, in patients that are H. pylori negative, the most common single cause of duodenal ulcers is the use of NSAIDS.¹³

The sponsor submitted two protocol amendments to the Statistical Analysis Plan. Because these endpoints were added towards the end of the study, it is not recommended to have these endpoints be included in the labeling. However, it is worth mentioning that results for Vimovo were favorable. Results from the Key Secondary Endpoints are included in the table below. (See Section 7.5.2 also)

Table 24 Key Secondary Endpoints Primary Safety Population (Trials PN400-301 and PN400-302)

	PN 400-301		PN400-302	
	Vimovo N = 218	Naproxen N = 216	Vimovo N = 210	Naproxen N = 210
Key Secondary Endpoint				
Pre-specified NSAID Associated Upper GI adverse events and/or Duodenal Ulcer	52.3%	69.0%	54.3%	71.9%
Discontinuation due to Pre-specified NSAID associated Upper GI adverse events or Duodenal ulcer	3.2%	12%	4.8%	11.9%
Incidence of Duodenal Ulcers at 6 months	0.5%	5.1%	1.0%	5.7%

Reviewer's Table Adapted from Sponsor's Table

In both trials, more patients taking EC naproxen (5.1% for Trial PN400-301 and 5.7% for trial PN400-302) developed duodenal ulcers than those taking Vimovo (0.5% and 1.0% respectively). More patients taking EC Naproxen also discontinued due to a pre-specified NSAID associated UGI AE or duodenal ulcer.

6.1.6 Other Endpoints

A number of other non-key secondary endpoints were also chosen that included:

- The proportion of subjects with heartburn resolution
- The response on Overall Treatment Evaluation-Dyspepsia (OTE-DP rating)
- The mean change from baseline for each of the Severity of Dyspepsia Assessment (SODA) subscales)
- The proportion of subjects discontinuing from the study due to an AE.

Other efficacy endpoints were summarized:

- Incidence of gastroduodenal ulcers at any time throughout 6 months of treatment by low-dose aspirin use (yes/no at randomization).
- Incidence of gastroduodenal ulcers at anytime throughout 6 months of treatment.

As stated above, it is not recommended that these non-key efficacy and tolerability endpoints be included in the labeling. However, it is worth noting that resolution of heartburn was analyzed for those patients with heartburn severity at baseline. More patients in the Vimovo group (76.1%) achieved heartburn resolution at 6 months compared with those in the Naproxen group (53.8%). Outcomes from the OTE-DP ratings were also better in patients that took Vimovo relative to those that took Naproxen. More patients taking Vimovo reported improved upper abdominal pain or discomfort (44.3%) than those who took Naproxen (31.1%) The SODA scores for pain, non-pain symptoms, and satisfaction were also improved in patients taking Vimovo compared to those taking Naproxen in both trials. Again these results have not been confirmed to be statistically significant and should not be considered scientifically valid.

6.1.7 Subpopulations

Several risk factors (including patient age, co-morbidities, concurrent medications, prior medical history and H. Pylori infection) have been demonstrated in a variety of studies with a fair amount of consistency to increase the risk of NSAID-associated GI injury. Risk factors for NSAID-related GI complications include a previous GI event (especially if complicated), age, chronic debilitating disorders (especially cardiovascular disease), high dose NSAID therapy and concomitant use of anticoagulants, corticosteroids or other NSAIDs including low-dose Aspirin.

The sponsor analyzed the primary efficacy endpoint by low-dose aspirin use (Yes/No), race, gender, ethnicity, age ≥ 60 , age < 60 , and smoking status (Yes/No). Overall for

the subgroup analysis, more ulcers were experienced by patients in the Naproxen arm relative to the Vimovo arm. The results of the analysis for low-dose aspirin use are presented in the statistical reviewer's table below. Overall the protective effect of Vimovo in preventing gastric ulcers after 6 months of use was maintained despite concurrent low-dose aspirin use. A larger effect size was seen in study PN400-302 than in PN400-301. However, conclusions about the effect size are difficult given the small number of patients taking low dose aspirin in the treatment arms for both studies. See Figure 12 below. Results are not statistically significant.

Table 25 Proportion of ITT Population: Trials PN400-301 and PN400-302 with Gastric Ulcer at 6 Months By Low-Dose Aspirin Use

	PN400-301		PN400-302		Combined	
	PN 400	Naproxen	PN 400	Naproxen	PN 400	Naproxen
LDA use (Yes)						
N	53	51	46	51	99	102
Gastric Ulcer	1 (1.9%)	12 (23.5%)	2 (4.3%)	17 (33.3%)	3 (3.0%)	29 (28.4%)
Gastric Ulcer Free	52 (98.1%)	39 (76.5%)	44 (95.7%)	34 (66.7%)	96 (97.0%)	73 (71.6%)
Maintained gastric ulcer free	45 (84.9%)	25 (49.0%)	31 (67.4%)	16 (31.4%)	76 (76.8%)	41 (40.2%)
Discontinued gastric ulcer free	7 (13.2%)	14 (27.5%)	13 (28.3%)	18 (35.3%)	20 (20.2%)	32 (31.4%)
Difference (95% CI ^a) of (EC naproxen – PN 400)	21.6% (9.9%, 35.6%)		29.0% (14.4%, 43.6%)		25.4% (16.1%, 35.3%)	
LDA use (No)						
N	165	165	164	159	329	324
Gastric Ulcer	8 (4.8%)	38 (23.0%)	13 (7.9%)	34 (21.4%)	21 (6.4%)	72 (22.2%)
Gastric Ulcer Free	157 (95.2%)	127 (77.0%)	151 (92.1%)	125 (78.6%)	308 (93.6%)	252 (77.8%)
Maintained gastric ulcer free	126 (76.4%)	78 (47.3%)	105 (64.0%)	86 (54.1%)	231 (70.2%)	164 (50.6%)
Discontinued gastric ulcer free	31 (18.8%)	49 (29.7%)	46 (28.0%)	39 (24.5%)	77 (23.4%)	88 (27.2%)
Difference (95% CI ^a) of (EC naproxen – PN 400)	18.2% (11.1%, 25.8%)		13.5% (5.9%, 21.4%)		15.8% (10.7%, 21.2%)	

Source: Statistical Reviewer's Table

CI: Confidence Interval

^a Exact Confidence Interval

The sponsor's subgroup analyses were validated by the statistical reviewer. The following figure provides a look at the cumulative proportion of gastric ulcers by risk factor. Vimovo appeared to have a larger effect relative to Naproxen for both patients with older age and for those with a previous history of ulcer use. This is important because patients ≥ 50 years old did not require a history of ulcer prior to enrollment, while patients <50 year old did. This creates the potential for confounding in the cumulative outcome results. Patients with a history of peptic ulcer in the past 5 years, were a small proportion of the combined dataset (69 total). Those patients with a history of peptic ulcer randomized to EC Naproxen (17 of 36, 47.2%) developed ulcers at a higher rate by the end of 6 months relative to those taking Vimovo (3 of 33, 9.1%). Given the small sample size for this subanalysis, no conclusions can be made.

Table 26 Cumulative Proportion of Study Enrollees with Gastric Ulcers at 6 months by Risk Factors, Combined Trials PN400-301 and PN400-302

Risk Factor	Vimovo	EC Naproxen
	N % Gastric Ulcer (95% CI)	N %Gastric Ulcer (95% CI)
Used Low Dose Aspirin*	99 3.0% (0.6-8.6)	102 28.4 (19.9 – 38.2)
Did not use Low Dose Aspirin*	329 6.4 (4.0 – 9.6)	324 22.2 (17.8 – 27.1)
History of Ulcer – 5 years	33 9.1 (1.9 – 24.3)	36 47.2 (30.4-64.5)
No History of Ulcer – 5 years	395 5.3 (3.3 – 8.0)	390 21.5 (17.6 – 26.0)
Age < 60 years *	216 8.3 (5.0 – 12.9)	217 21.2 (16.0 – 27.2)
Age ≥ 60 years*	212 2.8 (1.0 – 6.1)	209 26.3 (20.5 – 32.8)
Age ≥ 50 years/ no history of ulcers	393 5.1 (3.1 – 7.8)	390 21.5 (17.6 – 26.0)
Age ≥ 50 years/history of ulcers	21 4.8 (0.1 – 23.8)	27 55.6 (35.3 – 74.5)
Age ≥ 50 years and use of Low Dose Aspirin	96 3.1 (0.6 – 8.9)	100 29 (20.4 – 38.9)
History of Ulcer and use of Low Dose Aspirin	12 0 (0 – 26.5)	10 60 (26.2 – 87.8)

Sponsor's Table p.52/372 Integrated Summary of Efficacy *P<0.001 between groups, †P = 0.002 CI = Confidence Interval
 PN400=Vimovo

The medical reviewer also performed her own exploratory analysis on the cumulative incidence of gastric ulcers in patient that were ≥ 65 years old \pm low-dose aspirin use. By current guidelines for NSAID-induced GI toxicity, this group would be considered a high risk group for ulcer related complications.¹¹ The results are presented in the table below.

Table 27 Cumulative Proportion of Study Participants ≥ 65 years old \pm Low Dose Aspirin Use who developed Gastric Ulcers.

	PN 400 – 301 N = 434				PN 400 – 302 N = 420			
	Vimovo only N = 51	Vimovo + Aspirin N = 23	Naproxen only N = 49	Naproxen+ Aspirin N = 23	Vimovo only N = 41	Vimovo + Aspirin N = 19	Naproxen only N = 35	Naproxen + Aspirin N = 16
Ulcer Count Month 1	0 (0.0%)	0 (0.0%)	9 (18.37%)	5 (21.74%)	0 (0.0%)	0 (0.0%)	4 (11.43%)	5 (31.25%)
Ulcer Count Month 3	0 (0.0%)	0 (0.0%)	11 (22.45%)	7 (30.43%)	1 (2.44%)	0 (0.0%)	5 (14.28%)	6 (37.50%)
Ulcer Count Month 6	0 (0.0%)	0 (0.0%)	12 (22.49%)	9 (39.13%)	1 (2.44%)	1 (5.26)	7 (20.0%)	7 (43.75%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A fixed dose of Vimovo containing 500mg of Naproxen and 20 mg of Esomeprazole was used during the Phase III trials. Please see the clinical pharmacology review for more information. Also see Section 7.2.2 below.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

While patients taking Vimovo, did have fewer gastric ulcers than those taking Naproxen, increased exposure to both Vimovo and Naproxen lead to an increase in GI related side effects over time. Theoretically, the therapeutic effects of treatment with NSAIDs may decline over time, if patients discontinue use due to the side effects. Results of the survival analysis for EC Naproxen are consistent with this. However this occurred to a

lesser extent with Vimovo. Based upon review of the sponsor's survival analysis, after 3 months, there appears to be no substantial evidence of loss of the gastro-protective effect of Vimovo over time. (See Figures 14 and 15 below).

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

Safety Summary

A complete safety review of Vimovo was performed. A total of 1326 study participants were exposed to at least one dose of the Vimovo tablet at the highest strength that is to be used in clinical practice. Of these 1326 study participants, 1166 were exposed during Phase II and Phase III clinical trials and 135 took the drug for at least 348 days. A total of 352 study participants were exposed for at least 180 days. While the current clinical development program falls short of ICH exposure guidelines, one must also consider in the overall evaluation that there is a large amount of data available from prior clinical experience with the individual reference listed drugs. There was only 1 dose of Vimovo tablets (500mg naproxen/20mg esomeprazole) studied during the Phase III trials. However, the sponsor proposes to market an additional tablet containing 375mg naproxen/20mg esomeprazole.

The safety assessment was based upon data from the 6 Phase III trials. The pooling of clinical trials for the safety analysis appears appropriate. Trials that were of similar design, duration, population, and treatment exposures were grouped together in the Primary and Supportive Safety Population. Additionally, data from 5 of the Phase III trials was pooled into the Expanded Safety Population. The trial that was excluded from this Expanded Safety Population contained information on 9 patients from a trial that was terminated due to poor enrollment. The demonstrated safety profile for Vimovo was acceptable when compared to placebo. Commonly occurring adverse events were consistent with those in the currently approved labels of the individual reference listed drugs that make up the Vimovo tablet.

The medical reviewer had some questions regarding the dose of esomeprazole chosen for the Vimovo tablet (See section 7.2.2.) There were concerns regarding Vimovo also on the following issues:

- Risk of hepatic injury (Section 7.3.5)
- Adverse events with increasing dose exposure (Section 7.5.1)
- Risk of cardiovascular adverse events (Sections 7.4.1 and 7.5.2 and 7.5.3)

Patients taking Vimovo experienced more gastrointestinal related adverse events with increasing dose exposure. However, overall patients taking Vimovo still had fewer GI side effects than those taking Naproxen (63.6% vs. 80.3%) in the primary safety population. Additionally increased exposure was associated with more upper respiratory tract infections, peripheral edema and hypertension. This was somewhat anticipated based on the current labeling of the reference listed drugs.

One could reasonably anticipate that Vimovo will be used in older patients with a number of co-morbidities. Having a prior cardiovascular history appeared increased the risk of having a cardiac event while taking Vimovo. However, there was no significant difference between the two groups of the primary safety population in the percentages reporting a cardiac adverse event (2.4% Vimovo vs. 2.2% Naproxen). The medical officer reviewed case report forms for a subgroup of the patients experiencing cardiovascular events. No conclusions could be drawn about whether the cardiac event could be attributed to the study drug or to other underlying concurrent medical conditions experienced by the patient. Only 1 patient over the clinical development program had an acute myocardial infarction. Two patients experienced cerebrovascular accidents and two had transient ischemic attacks. As stated prior, all of these patients had complicated past medical histories therefore the associated risk of these events with Vimovo is probably no more than that of the currently marketed Naproxen. The adverse event profile otherwise did not appear to be significantly affected by race, ethnicity or gender or age.

There were no cases meeting the criteria for Hy's Law over the course of the clinical development. However, the reviewer was concerned about a few cases of marked AST and ALT elevations that occurred. Notwithstanding, cases of fatal hepatic injury have already been documented with Naproxen use. It is perhaps prudent to suggest that physicians monitor hepatic enzymes within the first 2 months of starting Vimovo. The medical officer also suggests very close monitoring of blood chemistries, throughout the duration of drug use and especially within the first 2months.

Table 28 Table of Overall Safety Review of Vimovo Tablets

	PN400 N = 1166	DR Naproxen N = 426	Celecoxib N = 488	Misopros tol N= 11	Placebo N= 246
Deaths	0	0	0	0	0
Study participants with at least 1 SAE	34 (2.9%)	14 (3.3%)	9 (1.8%)	0	1 (0.4%)
Study participants with discontinuations due to AEs	142 (12.2%)	173 (40.6%)	38 (7.8%)	6 (54.5%)	12 (4.9%)
Study participants with at least 1 treatment emergent adverse events	778 (66.7%)	373 (87.6%)	242 (49.6%)	8 (72.7%)	126 (51.2%)

Reviewers Table

Overall, there were no deaths. It appears that a disproportionately larger number of study participants discontinued from the Naproxen arm. However, these numbers also included those who discontinued from the pivotal trials due to development of a gastric or duodenal ulcer. Per protocol, these patients were considered “completers” and dropped from the trial.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

To support the safety of Vimovo, the sponsor submitted data from 13 clinical trials (7 trials in normal healthy volunteers and 6 trials in patients having one of the conditions in the proposed indication). Table 4 above provides descriptive information for all the individual clinical trials in this submission. It should be noted that trial PN400-303, was designed to assess the efficacy of Vimovo tablets for reducing gastric ulcers in a high-risk population. However, this study was terminated early because of problems with enrollment. An overview of the trials was presented above in Table 4.

For the safety analysis data was pooled from trials in the development program as outlined in Table 8 below. The pooled populations included the Primary Safety Population, the Supportive Safety Population, the Expanded Safety Population, the Osteoarthritis Safety Population, the 6 month long term safety population and the 12 month long term safety population. The pooling of clinical trials for the safety analysis appears appropriate. Trials that were of similar design, duration, population, and treatment exposures were grouped together in the Primary and Supportive Safety Population. The Primary Safety Population consisted of patients from trials PN400-301 and PN400-302, pivotal trials in assessing the efficacy of Vimovo tablets at reducing the risk of ulcer occurrence at 6 months. The Supportive Safety Population consisted of patients from trials PN400-307 and PN400-309, trials designed to provide information on the treatment of signs and symptoms of osteoarthritis in identical populations with 3 months of exposure to Vimovo, celecoxib, or placebo.

The Expanded Safety Population consisted of patients from all the Phase III trials. Within the Expanded Safety Population, 4 of the 5 trials were randomized, double-blind, active or placebo controlled trials with repeated dose testing. The final trial within Expanded Safety Population was the one year open label trial of Vimovo tablets. The Expanded Safety Population provides the largest pool of patients. The Expanded Safety Population does not include information from the seven Phase I clinical trials in healthy volunteers. Additional safety data from single dose and short-term multiple dose trials done in normal healthy volunteers was provided separately by the sponsor. The sponsor also provided a limited amount of postmarketing data and information from the literature as secondary sources in support of the safety of the Vimovo tablet.

Table 29 Pooled Populations for Safety Analysis

Name of Integrated Pools and Populations						
	PSP (Primary)	SSP (Supportive)	ESP (Expanded)	OAP (Osteoarthritis)	SMP (6 Month)	LSP (Longterm)
Trials	PN400-301 PN400-302	PN400-307 PN400-309	PN400-301 PN400-302 PN400-307 PN400-309 PN400-304	PN400-301 PN400-302 PN400-307 PN400-309 PN400-304	PN400-301 PN400-302 PN400-304	PN400-304
Total Number of Participants Exposed in Each Population by Treatment						
Treatment						
PN400	428	490	1157	951	491	239
EC Naproxen	426				220	
Celecoxib		488				
Placebo		246				

Reviewers Table Adapted from Sponsor's Table 5.3.5.3 2.2 p 14/2911 Integrated Safety Summary

7.1.2 Categorization of Adverse Events

Per the sponsor, all adverse events (AEs) were coded using MedDRA version 10.1 and classified by system organ class (SOC) and preferred term. The appropriateness of the applicant's coding was assessed by comparing the preferred terms to the verbatim terms recorded by investigators within a sampling of case report forms and adverse event dataset. In general the coding appeared to be accurate. There was some splitting and lumping of preferred terms. When appropriate, the medical officer combined preferred terms. For example, the terms increased blood pressure and hypertension were combined. For the purpose of analysis, the term verbatim heartburn was coded to the preferred term dyspepsia throughout the submitted datasets.

Per the sponsor, an adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A pre-existing condition or signs or symptoms present at the time of study medication administration were not considered an adverse event. In addition, signs or symptoms associated with the disease/condition/indication being evaluated as part of assessments of study medication efficacy were in general not to be recorded as adverse events unless they worsened in severity.

A serious adverse event was defined as an event that

1. was fatal or a life-threatening event;

A "life-threatening" event was present when the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred.

- Note that this definition does not include an event that, had it occurred in a more serious form, might have caused death;
2. results in persistent or significant disability/incapacity;
 3. constitutes a congenital anomaly/birth defect;
 4. requires inpatient hospitalization or prolongation of existing hospitalization unless hospitalization is for
 - a) routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
 - b) elective hospitalization for treatment of a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug;
 - c) treatment on an emergency outpatient basis for the event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
 - d) social reasons and respite care in the absence of any deterioration in the subject's general condition;
 5. is medically significant, that is defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Per the sponsor the pooling of the studies within the development program was designed to provide comparisons of the largest number of similarly exposed study participants from across the studies from the appropriate treatment arms.

In general, trials that were of similar design, duration, population, and treatment dosing regimen were grouped together. Table 8 above outlines the pooled populations used in the safety analysis. Please refer to section 7.1.1 for more information. In the opinion of the medical officer, the pooling of populations seems appropriate.

7.2 Adequacy of Safety Assessments

All trials submitted in the clinical development program employed standard assessments of safety. No drug interaction studies were performed during this clinical development program. Per the sponsor "there are no known interactions between naproxen and esomeprazole that would indicate any novel adverse pharmacology, toxicology, physical or chemical interaction or tolerability issues as a result of their combination." Given the known safety issues associated with currently available formulations of naproxen and esomeprazole, the safety evaluations performed as part of the development program seem appropriate and reasonably applicable to assess the safety of the drug.

Traditionally in evaluating NSAID toxicity one would want to pay particular attention to gastrointestinal events, cardiovascular events including elevations in blood pressure, renal complications, liver toxicity (i.e. transaminase elevations), and hematological events (i.e. anemia). During the pivotal studies PN400-301 and 302, the sponsor performed endoscopy and routinely monitored laboratory parameters, and physical exam findings to assess the safety of the drug. For the majority of the studies, electrocardiograms (ECGs) were performed only at screening to determine eligibility. However, in the long term study PN400-304, ECGs were performed as part of screening, at the 6 month visit, and at the final 12 month visit or early termination visit.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

To evaluate the adequacy of clinical experience with a new drug, the reviewer referred to the ICH-E1A guidance “The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.” This guideline recommends that 300 to 600 participants be treated for 6 months at dosage levels intended for clinical use; 100 participants be exposed for at least 1 year, and a total of 1500 participants be exposed to the new drug.

The table below provides the number of individual study participants exposed to each treatment in the drug development program.

Table 30 Enumeration of Study Participants for New Drug Development Program

Enumeration of Subjects for New Drug Development Program NDA 22511						
Clinical Trials Groups	Treatment Groups					
	Vimovo 500mg/ 20mg	Vimovo 375mg/ 20mg	Active Control (EC Naproxen)	Active Control (Celecoxib)	Active Control (Misoprostol)	Placebo
Completed Phase 1 (Clinical Pharmacology)						
Single Dose	70	30				
Multiple Dose	90					
Total	160		94			
Completed Phase 2-3 (Clinical Trials for Proposed Indication)						
	1166 [±]		426	488	11	246

[±]Includes 9 study participants from Study PN400-303 with Misoprostol which was terminated early due to low enrollment.
 Reviewer's table Adapted from Sponsor Table 5.3.5.3.2.1 Integrated Summary of Safety p11/2911

During the Phase I and Phase III clinical trials, a total of 1326 study participants were exposed to at least one dose of the Vimovo tablet that is to be used in clinical practice. Of these 1326 study participants, 160 were exposed during the Phase I trials and 70 of those were exposed to a single dose. One hundred thirty five (135) took the study drug for 1 year (defined as at least 348 days) and 352 took the drug for at least 180 days. Based the number of participants exposed to the drug for 6 months and 1 year, there seems have been adequate exposure to assess the clinical safety of the new drug.

The table below shows the number of study participants who received Vimovo by duration of exposure and total doses taken. All study participants in this table received the study drug containing 20mg of esomeprazole combined with 500mg of delayed released naproxen.

Table 31 Number of Study Participants Exposed to Vimovo by Duration of Study Drug Exposure and Total Doses Taken

Total Doses Taken	Duration of Study Drug Exposure (Days)						Total
	1	2 - 14	15-30	31-90	91-181	>180	
1	79	1	0	0	0	0	80
2-28	0	104	8	9	1	0	122
29-60	0	1	48	10	1	0	60
61-80	0	1	6	461	34	1	503
181-360	0	0	0	13	185	99	297
>360	0	0	0	0	12	252	264
Total	79	107	62	493	233	352	1326

Study participant demographics for selected pooled populations are outlined in Demographic Table below. The primary safety population was predominantly white and female. The age distribution appeared to be balanced between treatment groups and the median age was approximately 59 years. There was also a fairly equal distribution across treatment arms of study participants who were taking low dose aspirin or had a history of an upper gastrointestinal problem. More study participants in the Vimovo group has a history of cardiovascular disease than those in the EC Naproxen Group. This may have important implications in our safety evaluation, if the data show that more patients taking Vimovo experience cardiac events relative to the EC Naproxen control.

Like the primary safety population, study participants in the supportive safety population were predominantly white and female with a median age of approximately 61 years old. Low dose aspirin use was slightly higher among study participants who took Vimovo (25.3%) compared to those that took Celecoxib (21.3%) and placebo (22.8%). Approximately 30.5% of study participants taking Celecoxib had a history of an upper gastrointestinal disorder. This was slightly less than the Vimovo (34.3%) and placebo arms (34.1%). However, there were fewer patients with history of cardiovascular disease in the Vimovo (54.1%) and placebo groups (55.1%) compared to the Celecoxib group (57%).

Demographics in the Twelve-Month Population (TMP) are generally comparable to the Primary Safety Population (PSP) and the secondary safety population (SSP) in that they were predominantly white, female and had a median age of approximately 60 years.

The Expanded Safety Population (ESP) included study participants assigned to the Vimovo treatment group from the combined primary safety population and the secondary safety population. The ESP was predominantly white, female, non-Hispanic and had a median age of 60 years. Just over a quarter of patients in the ESP used low dose aspirin (25.7%). Over half (51.9%) of the study participants entered the study with a history of Upper GI disorders and 56.4% had a history of cardiovascular disease.

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Table 32 Demographic Data From Selected Pooled Populations.

	Primary Safety Population Trials 301 and 302		Supportive Safety Population Trials 307 and 309			Expanded Safety Population (PSP + SSP+ Longterm Safety Trial)	Twelve Month Safety Population (Completed Long Term Safety Trial)
	Vimovo (n=428)	EC Naproxen (n=426)	Vimovo (n=490)	Celecoxib (n=488)	Placebo (n=246)	Vimovo Only Patients (n=1157)	Vimovo Only (n=135)
Age (Years): Mean (std) Median Min, Max	60.2 59 27,90	60.6 59 29,90	62.1 61 50,88	61.9 60.5 49,90	61.6 60.0 50,87	61.1 60.0 27,90	60.7 60.0 44,86
Age Group <60 years <50 years 50 - 59 yrs ≥60 years	216 14 202 212	217 9 208 209	206 0 206 284	225 1 224 263	111 0 111 135	541 21 520 616	67 68
Sex Male Female	146 282	135 291	170 320	187 301	87 159	387 770	42 93
Race White Black Asian	367 53 5	371 49 4	386 83 20	392 79 12	199 39 6	964 160 29	119 14 2
Ethnicity Hispanic/Latino Non Hispanic	83 345	78 348	32 458	36 452	16 230	157 1000	25 110
Low Dose Aspirin Use Yes No	99 329	102 324	124 366	104 384	56 190	297 860	95 40
UGI History Yes No	293 135	300 126	168 322	149 339	84 162	601 556	80 55
Cardiovascular History Yes No	245 183	229 197	265 225	109 278 210	132 114	652 505	74 61

7.2.2 Explorations for Dose Response

Dose ranging studies were performed in normal healthy volunteers. Please see the clinical pharmacology review for greater details on the Phase I trials conducted in healthy volunteers. Doses for naproxen in the proposed formulation of Vimovo match currently approved and marketed doses for NAPROSYN® and NEXIUM®. At present, the currently approved dosing regimen of Nexium® for the risk reduction of ulcers is 20mg or 40mg once daily for up to 6 months.

In Phase I trials, the sponsor studied Vimovo tablets containing 10mg, 20mg, and 30mg doses of esomeprazole. Pharmacodynamic responses of pH control were evaluated in study PN400-104. Direct measurement of protection against gastrointestinal lesions caused by naproxen administration, were evaluated using the Lanza score in PN400-101.

Per the sponsor, after 9 days of treatment, patients taking Vimovo tablets that contained either 30mg or 20mg of esomeprazole (given twice a day) experienced a greater percentage of time with intragastric pH>4.0 than the treatment group taking Vimovo tablets containing 10mg of esomeprazole. The sponsor also maintained that their trial showed treatment with Vimovo tablets containing 20mg and 30 mg of esomeprazole resulted in a greater percent of time with intragastric pH>4.0 than the treatment group given a regimen of Naproxen® 500mg twice a day plus concomitant Nexium® 20mg once a day. The latter is one of the currently approved dosing regimens for the separate Naproxen® and Nexium® drugs.

The sponsor states that “based on pH control and prevention of naproxen induced upper GI lesions, Vimovo tablets containing 20mg esomeprazole were determined to be the most appropriate to study in pivotal studies in subjects at risk for NSAID-associated gastric ulcers.” The sponsor considered this the lowest effective dose. However, it is not completely clear to the medical officer why no pivotal studies were conducted with Vimovo tablets containing 10mg. The sponsors, themselves, stated that the reduction in gastroduodenal injury (based on Lanza score) showed an “insignificant esomeprazole dose-dependent trend” despite similar naproxen levels in all treatment groups. No Lanza score grade 3 or 4 erosions were found in any study participant in the three Vimovo treatment arms containing 10mg, 20mg, and 30mg of esomeprazole. Furthermore, while hydrogen ion secretion may be higher than normal in duodenal ulcers, hydrogen ion secretion is lower than normal in gastric ulcers, not higher than normal as might be assumed. Therefore one might assume that a lower dose of the proton pump inhibitor could be effective. Additionally studies using intragastric pH > 4 were done to demonstrate optimal conditions to achieve healing and symptomatic relief of GERD not ulcers.

The table below summarizes the number of study participants exposed to Vimovo containing 500mg of naproxen and 20mg of esomeprazole in the clinical development program.

Table 33 Number of Study Participants who Took Vimovo Tablets (500/20mg) by Duration of Study Drug Exposure and Total Number of Doses Taken for All Clinical Trials

Total Doses Taken	Duration of Study Drug Exposure (Days)						Total
	1	2 - 14	15-30	31-90	91-181	>180	
1	79	1	0	0	0	0	80
2-28	0	104	8	9	1	0	122
29-60	0	1	48	10	1	0	60
61-80	0	1	6	461	34	1	503
181-360	0	0	0	13	185	99	297
>360	0	0	0	0	12	252	264
Total	79	107	62	493	233	352	1326

Source: Reviewers table adapted from Sponsor's table p.25/2911

7.2.3 Special Animal and/or In Vitro Testing

The sponsor is relying on previous findings of safety and publicly available information on the toxicology of both naproxen and esomeprazole for the current application. During the End of Phase 2 meeting, the Agency agreed that no additional non-clinical pharmacology, pharmacokinetic, or toxicology studies would be required. Please see the pharmacology/toxicology review for any additional information on this section.

7.2.4 Routine Clinical Testing

Safety assessments performed in adult clinical trials included vital signs, ECG, hematology, clinical chemistries (including ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, and creatinine), and clinical assessments. Standard assessments for treatment emergent adverse events (TEAEs) were done in addition to pre-specified NSAID-associated UGI adverse events and protocol required-endoscopy (studies PN400-301 and PN400-302). Overall the safety testing for the adult clinical program appears adequate to assess the primary safety concerns associated with NSAIDs and PPIs.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please section 4 above. Coadministration of the naproxen and esomeprazole did not alter the pharmacokinetic profile of either drug.

Details of metabolic assessments will be found in the clinical pharmacology review. Please refer to the review done by Drs. Jane Bai and Dilara Jappar.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events associated with the use of NSAIDs and PPIs have been studied and reported extensively in the literature. Please see section 2.4 above. The labeling of all NSAID products includes a Medication Guide and a Boxed Warning highlighting the potential for increased risk of cardiovascular events and the serious potentially life-threatening gastrointestinal bleeding associated with their use.

To address possible cardiovascular serious adverse events and other cardiovascular treatment emergent adverse events, a separate Cardiovascular Endpoint Committee was established. The Cardiovascular Endpoint Committee used the Anti-platelet Trialist Collaborative (APTC) defined endpoints and other non-APTC major adverse cardiovascular events (MACE) to achieve its goal.

An independent gastrointestinal adjudication committee (GI-IAC) was established to review and adjudicate all clinically significant gastrointestinal adverse events that developed during the Phase 3 development program.

7.3 Major Safety Results

Five phase 3 studies were submitted in support of the safety of Vimovo tablets.

7.3.1 Deaths

There were no deaths in any of the trials submitted in support of this NDA.

7.3.2 Nonfatal Serious Adverse Events

Per the sponsor, a serious adverse event was defined as an event that:

1. was fatal or a life-threatening event;
A "life-threatening" event was present when the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. Note that this definition does not include an event that, had it occurred in a more serious form, might have caused death;
2. results in persistent or significant disability/incapacity
3. constitutes a congenital anomaly/birth defect;
4. requires inpatient hospitalization or prolongation of existing hospitalization unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
 - elective hospitalization for treatment of a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for the event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
 - social reasons and respite care in the absence of any deterioration in the subject's general condition;
5. Is medically significant, that is defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

There were no Serious Adverse Events reported in the Phase 1 studies. There were 58 Serious Adverse Events reported from 53 study participants in the six Phase 3 clinical trials. The numbers of SAEs in all of the Phase 3 trials are outlined in the table below.

Table 34 Number of SAEs in All of the Phase 3 Trials by Treatment Group

Treatment	PN400 N = 1166	DR Naproxen N = 426	Celecoxib N = 488	Misoprostol N= 11	Placebo N= 246	Overall Total
Study	Number of SAEs					
PN400-301	6	6	0	0	0	12
PN400-302	5	8	0	0	0	13
PN400-303	0	0	0	0	0	0
PN400-304	15	0	0	0	0	15
PN400-307	5	0	6	0	0	11
PN400-309	3	0	3	0	1	7
Total	34	14	9	0	1	58

Reviewers Table adapted from Sponsor's Table Submitted in response to Information Request.

Overall the frequency of serious adverse events (SAEs) was 2.9% in the Vimovo group, 3.3% in the Naproxen group, 1.8% in the Celecoxib group, 0% in the Arthrotec group and 0.4% in the placebo group. The case report forms and narratives of the SAEs for studies PN400-301, PN400-302, and PN400-304 were reviewed. Details for each of the SAEs in PN400-301, PN400-302, and PN400-304 can be found in section 5.3 above. The most common reported SAE for the pivotal trials 301 and 302 were in the SOC of Cardiac Disorders (1.2%). The frequency of cardiac disorders was 0.5% for both the Vimovo group and the Naproxen group respectively and 0.2% for the Celecoxib group.

There were 3 cases of atrial fibrillation/flutter in the Vimovo group and none in the other treatment groups. (There was also 1 case of premature ventricular contractions in the Vimovo group but this did not qualify to be an SAE). It is the opinion of the medical officer that none of the cardiac SAEs can be causally related to the study drug.

The following table provides a line listing of all SAEs in Phase 3 clinical trials of the development program.

Table 35 Summary of Serious Adverse Events All Phase III Trials

System Organ Class/ Preferred Term	Vimovo (N=1166)	Naproxen (N=426)	Celecoxib (N=488)	Misoprostol (N=11)	Placebo (N=246)
Number of Study Participants with Any Serious Adverse Events	31 (2.7%)	13 (3.1%)	8 (1.6%)	0	1 (0.4%)
All Serious Adverse Events	34	14	9	0	1
Cardiac Disorders	6 (0.5%)	2 (0.5%)	1 (0.2%)	0	0
Coronary artery disease	1 (<0.1%)	1 (0.2%)	1 (0.2%)	0	0
Atrial Flutter	2 (0.2%)	0	0	0	0
Unstable Angina	1 (<0.1%)	0	0	0	0
Atrial Fibrillation	1 (<0.1%)	0	0	0	0
Complete AV Block	1 (<0.1%)	0	0	0	0
Myocardial Infarction	1 (<0.1%)	0	0	0	0
Palpitations	0	1 (0.2%)	0	0	0
Infections and Infestations	4 (0.3%)	4 (0.9%)	1 (0.2%)	0	0
Pneumonia	2 (0.2%)	1 (0.2%)	0	0	0
C. difficile colitis	0	1 (0.2%)	0	0	0
Diverticulitis	0	1 (0.2%)	0	0	0
Gangrene	0	0	1 (0.2%)	0	0
Necrotizing fasciitis	1 (<0.1%)	0	0	0	0
Post procedural infection	0	1 (0.2%)	0	0	0
Staphylococcal infection	1 (<0.1%)	0	0	0	0
Urinary tract infection	0	1 (0.2%)	0	0	0
General disorders and administration site conditions	3 (0.3%)	1 (0.2%)	0	0	0
Non-cardiac chest pain	2 (0.2%)	1 (0.2%)	2 (0.4%)	0	0
Chest pain	1 (<0.1%)	0	0	0	0
Swelling	0	0	1 (0.2%)	0	0

System Organ Class/ Preferred Term	Vimovo (N=1166)	Naproxen (N=426)	Celecoxib (N=488)	Misoprostol (N=11)	Placebo (N=246)
Injury, poisoning and procedural complications	3 (0.3%)	3 (0.7%)	1 (0.2%)	0	0
Concussion	0	1 (0.2%)	0	0	0
Fracture	0	1 (0.2%)	0	0	0
Hip Fracture	1 (<0.1%)	0	0	0	0
Incisional hernia	1 (<0.1%)	0	0	0	0
Post procedural hemorrhage	1 (<0.1%)	0	0	0	0
Road Traffic Accident	0	0	1 (0.2%)	0	0
Upper limb fracture	0	1 (0.2%)	0	0	0
Musculoskeletal and connective tissue disorders	5 (0.4%)	0	1 (0.2%)	0	0
Osteoarthritis	3 (0.3%)	0	0	0	0
Back pain	1 (<0.1%)	0	1 (0.2%)	0	0
Musculoskeletal pain	1 (<0.1%)	0	0	0	0
Gastrointestinal disorders	4 (0.3%)	1 (0.2%)	0	0	0
Perforated appendicitis	1 (<0.1%)	0	0	0	0
Ischemic colitis	1 (<0.1%)	0	0	0	0
Duodenal ulcer hemorrhage	0	1 (0.2%)	0	0	0
Hematemesis	1 (<0.1%)	0	0	0	0
Acute pancreatitis	1 (<0.1%)	0	0	0	0
Nervous System disorders	4 (0.3%)	0	0	0	1 (0.4%)
Carotid artery stenosis (Transient Ischemic Attack)	2 (0.2%)	0	0	0	0
Cerebrovascular accident	1 (<0.1%)	0	0	0	0
Intracranial aneurysm	0	0	0	0	1 (0.4%)
Syncope	1 (<0.1%)	0	0	0	0

System Organ Class/ Preferred Term	Vimovo (N=1166)	Naproxen (N=426)	Celecoxib (N=488)	Misoprostol (N=11)	Placebo (N=246)
Immune system disorders	0	0	2 (0.4%)	0	0
Anaphylactic reaction	0	0	1 (0.2%)	0	0
Drug hypersensitivity	0	0	1 (0.2%)	0	0
Psychiatric Disorders	2 (0.2%)	0	0	0	0
Confusional state	1 (<0.1%)	0	0	0	0
Suicide attempt	1 (<0.1%)	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (<0.1%)	0	0	0	0
Thyroid cancer	1 (<0.1%)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	1 (0.2%)	0	0	0
Chronic Obstructive Pulmonary Dz	0	1 (0.2%)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (0.2%)	0	0	0
Diabetic ulcers	0	1 (0.2%)	0	0	0
Surgical and medical procedures	1 (<0.1%)	0	0	0	0
Mastectomy	1 (<0.1%)	0	0	0	0

Reviewers Table. Adapted from Applicant's Table S1.3, Integrated Summary of Safety pages 354-357

7.3.3 Dropouts and/or Discontinuations

Please refer to section 5 above for the dropout profile of pivotal studies PN400-301 and PN400-302. The dropout profile for the long-term trial PN400-304 is also detailed in section 5 above. The overall dropout profile for Phase 3 clinical trials is summarized in the table below.

Table 36 Dropout Profile for All Phase III Trials

Dropout Profile: Incidence of Dropout by Treatment Group and Reason for Phase 3 Clinical Trials with New Drug					
Reasons For Dropout	Treatment Groups				
	Vimovo N = 1166	Placebo N = 246	Naproxen N = 426	Celecoxib N=488	Misoprostol* N = 11
Adverse Event	142 (12.2%)	12 (4.9%)	173 (40.6%)	38 (7.8%)	6 (54.5%)
Withdrew Consent	84 (7.2%)	22 (8.9%)	31 (7.3%)	38 (7.9%)	1 (9%)
Lost to Follow-Up	22 (1.9%)	1 (0.4%)	9 (2.1%)	6 (1.2%)	3 (2.7%)
Other	53 (4.5%)	9 (3.7%)	11 (2.6%)	17 (3.5%)	0 (0%)
Total Dropouts	301 (25.8%)	44 (17.9%)	329 (77.2%)	99 (20.3%)	10 (90.9%)

*Reviewers Table * Trial PN400-303 discontinued prematurely due to poor enrollment .

Overall, a total of 33.5% (783) of study participants discontinued from clinical trials in the development program prior to completion. In the Vimovo group, 142 study participants experienced 146 adverse events. Interestingly there was a noticeable difference in the rate of discontinuations between the two trials (PN400-301 and PN400-302). (Details in Section 5.3 above) In the first trial (PN400-301) more patients withdrew from the Naproxen arm (30.5%) relative to the Vimovo arm (17.4%). However, in the second trial (PN400-302), the percentage of withdrawals was similar between the two arms (28.8% for Vimovo and 27.5% for Naproxen). This difference in rate of discontinuations between the two studies was largely driven by a difference in the number of patients that withdrew consent. More patients in PN400-301 withdrew consent from the Naproxen arm (11.4% versus 6.8% in the Vimovo arm), whereas in PN400-302 more patients withdrew consent from the Vimovo arm (11.3% versus 3.8% in the Naproxen arm). Per the sponsor, of the 24 patients that withdrew consent from Vimovo treatment in Study PN400-302, five indicated a lack of efficacy and seven did not want to undergo endoscopy. Section 5 above provides a summary of the reasons for withdrawal in Trial PN400-302.

Overall, more study participants discontinued from the phase 3 trials because of an adverse event in the Naproxen group (40.6%) than the Vimovo group (12.2%) and the celecoxib group (7.8%). However, these numbers also included those who discontinued from the pivotal trials secondary to development of a gastric ulcer or duodenal. The protocols for the pivotal trials (PN400-301 and PN400-302) clearly stated that study participants would be withdrawn from the trial for endoscopic confirmation of a gastric ulcer at any time during study drug treatment including at the 6 month visit. These study participants were considered “completers”. If a duodenal ulcer was detected at anytime during the study drug treatment, including the 6th month visit, the participant was also withdrawn (per protocol) and was not considered as completing the study. After gastric ulcer and duodenal ulcer, the most frequent adverse event leading to discontinuation was dyspepsia. The medical reviewer has some concern about the use of the term dyspepsia. As stated previously, clinically dyspepsia is a very broad term that can include a number of symptoms but it usually refers to pain in the upper or middle abdomen. Rome III criteria for functional dyspepsia is defined as at least 3 months, with onset at least 6 months previously of 1 or more of the following: bothersome post-prandial fullness, early satiation, epigastric pain, epigastric burning AND no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

In the opinion of the medical reviewer there was some splitting of the preferred terms that lead to discontinuation. In example of this, consider the terms abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, and abdominal tenderness. Likewise, the terms rash and generalized rash can be combined under one term. Notwithstanding, even when the reviewer collapsed these terms, there was no significant safety signals detected for the new drug. In example of this, when the medical reviewer combined the relevant aforementioned preferred terms into one category of abdominal pain, the incidence of abdominal pain was 1.1% in the Vimovo group, 1.9% in the Naproxen group, 1.0% in the Celecoxib group, and 0.4% in the placebo group.

Of those study participants that withdrew, the only preferred term that was reported in more than 1% of the 1166 study participants taking Vimovo was gastric ulcers, which was reported in 2.2%. The incidence of gastric ulcers was 23.7% in the naproxen group; 0%, in the celecoxib group and placebo group, and 9.1% in the misoprostol group. Please note that the higher percentage of gastric ulcers in the misoprostol group may be attributed to the small number of patients enrolled in that group.

Although more patients in the Vimovo group relative to the Naproxen and Celecoxib group, withdrew due to treatment emergent adverse events from the SOC of Investigations, there did not appear to be any significant dropouts from the elevations in blood pressure (0.3%), alterations in transaminases (0.2%) or changes in hematological parameters (0.3%). Likewise the dropout incidence in the Vimovo group due to cardiovascular problems (0.4%) and renal problems (<0.1%) was low. Comparisons of dropout rates are provided in the table below.

Of the 1166 study participants in the Vimovo treatment group, 4 (0.3%) patients discontinued due to blood pressure increase or hypertension (Patients PN400-302-544-2218, PN400-309-405-8538, PN400-309-452-8364, PN400-307-080-6360). Please see the table below for additional information on these patients.

Table 37 Patients Withdrawn from Vimovo Treatment Group Due to Elevated Blood Pressure or Hypertension

Patient Number	Narrative	Relatedness
PN400-302-544-2218	<p>69 year old White NonHispanic, male, nonsmoker. Past medical history significant for hypertension, hypercholesterolemia, s/p coronary artery bypass graft, arrhythmia, GERD, osteoarthritis, and mild depression. Medications included Zocor, Toprol, Flecainide, Lexapro, Aspirin. Per report, the patient had a baseline screening BP of 183/78 on 12/05/07 with a study baseline BP reading of 178/80. Study drug was dispensed on 12/19/07. On 1/21/08, the patient reported that his BP was worsening and requested withdrawal from the study. The patient withdrew from the study and took his last dose of study medication on 1/31/08. BP reading on that day was 115/70. However it was reported that the BP issue resolved on 1/28/08. There are no BP readings available for this date. Additionally, if this incident was related to study medication, then why did the BP lower prior to stopping the drug 3 days later. Because NSAID have been associated with fluid retention and elevated blood pressure, it is probable that this reaction probably is related to the study drug. However, in the opinion of the medical officer, there are several gaps in the history and more information is required before any conclusion can be made.</p>	Probable
PN400-309-405-8538	<p>71 year old White NonHispanic female nonsmoker. Past medical history included cardiac arrhythmia and osteoarthritis. Concomitant medications were atenolol and estrogen. Per report on 7/7/08 screening blood pressure was 140/60. Baseline reading was 122/76 on 7/24/08. Study drug was dispensed on 7/24/08. On 7/31/08 BP reading was 162/82. Repeat reading done on 8/7/08 was 170/70. This was the last day that study medication was taken by the study participant. The patient withdrew from the study 4 days later on 8/11/08. At that time BP was 140/60. Again very few details are provided. The medical officer questions the validity of the baseline BP reading. There are several factors that could have made this reading lower relative to the other readings (i.e. size of the cuff, different person performing the reading, etc.) It is possible that this was related to study medication, especially given the rapid rise after administration of the study drug and the quick return to baseline levels upon cessation of the drug. However no conclusions can be made.</p>	Possibly

Patient Number	Narrative	Relatedness
PN400-309-452-8364	63 year old Black NonHispanic Female nonsmoker. Past medical history included osteoarthritis, nephrolithiasis, GERD and s/p hysterectomy. Medications included aspirin and multivitamins. The patients has baseline BP 7/22/08 of 128/86. Study drug was dispensed this day. 7 days later patient had BP 124/82. 9/2/08 patient BP 116/84. Patient complained of dizziness and headache on 9/12/08. Consequently, study medication was discontinued and last dose was taken 9/12/08. Patient was withdrawn from the study 10/1/09. At that time BP reading was 144/90 and patient's headache and dizziness were still present.	Possibly
PN400-307-080-6360	68 year old Black NonHispanic Female nonsmoker. Past medical history included hypertension, hypothyroidism, myopia, cataracts, allergic rhinitis, gallstones (s/p cholecystectomy), GERD, prior TB exposure, and s/p hysterectomy. Medications included Amlodipine, premarin, and synthroid. At screening on 8/14/2008 BP was reportedly 120/80. Study drug was dispensed on 8/21/08. No vital signs were recorded on the CRF for this day. Reportedly on 8/22/08, the patient developed dizziness and moderate increase in blood pressure. However there is no record of this visit in the sponsor's submitted case report forms and the narrative does not indicate the extent of the "moderate increase". Reportedly the patient's last dose of study medication was on 8/24/08 and the patient was withdrawn from the study 8/28/08. At the time of withdrawal, the patient's BP was 110/72 and reportedly there was no dizziness. Again there are several details missing from the CRF and narrative, which is concerning.	Probable

While there were no patients in the naproxen, celecoxib, arthrotec, or placebo groups that experienced a drop in hemoglobin, four (0.3%) study participants in the Vimovo discontinued due to changes in hemoglobin (307-036-6505; 307-065-6295, 309-410-8325, 309-409-8254). Details for these patients are provided in the table below

Table 38 Discontinuations from Vimovo due to Drops in Hemoglobin or Anemia

Patient Number	Narrative	Relatedness
PN400-307-036-6505	Patient 6505 was a 63 year old White NonHispanic female nonsmoker with a history of elevated cholesterol, controlled hypertension, Type II Diabetes—non-insulin dependent, and asthma. Medications included pioglitazone, lisinopril, simvastatin, and glimepiride. At screening on July 1, 2008, the patient had a hemoglobin of 15.1 g/dl. Study medication was dispensed on July 15, 2008. On July 23, 2008, the patient’s hemoglobin was 13.0g/dl and continued to fall to 12.4 g/dl on August 27, 2008. The last dose of study medication was on September 2, 2008 and the patient withdrew from the study at that time. At the final visit on October 20, 2008, the patient’s hemoglobin has returned to baseline 15.1g/dl	Probable
PN400-307-065-6295	58 year old White, NonHispanic, Male, Nonsmoker with a past medical history significant for impaired fasting glucose, internal hemorrhoids with hemorrhoidal bleeding (s/p hemorrhidectomy—no date reported), gastritis, and dyslipidemia. Medications included ferrous sulfate, folic acid, ascorbic acid and cobalamin. Reportedly the screening hemoglobin on June 25, 2008 was 13.6 g/dl. Study drug was dispensed on Jul 2, 2008. Hemoglobin decreased to 11.1g/dl on August 13, 2008. Last dose of study medication taken on August 19, 2008. The patient withdrew from the trial the following day. Follow-up assessment done on September 17, 2008 reported a hemoglobin of 13.6 g/dl. In the opinion of the medical officer, there was a lot of information missing from the CRF and one had to depend largely on the narrative to piece the facts together. It is very possible that the drop in hemoglobin was related to study drug. However, given the patients history of internal hemorrhoids and bleeding, it is also possible that the patient had another possible source for the drop in hemoglobin. However the fact that the hemoglobin rebounded after study drug stopped increases the likelihood that this event was study drug related.	Possible

Patient Number	Narrative	Relatedness
PN400-309-410-8325	51 year old White, NonHispanic, female nonsmoker, postmenopausal. Past medical history significant for osteoarthritis, bilateral carpal tunnel, constipation, torn meniscus (s/p repair), chronic anemia, endometriosis and hyperlipidemia. Medications included Nexium and Ferrous Sulfate. At study screening on August 21, 2008, the patient's hemoglobin was 12.2 g/dl. Study drug was dispensed on September 4, 2008. Patient's hemoglobin on September 11, 2008 was 11.7g/dl. On October 16, 2008 hemoglobin was 11.2 g/dl and on October 21, 2008, hemoglobin was 10.4 g/dl. Last dose of study medication was taken on October 21, 2008 and the patient was withdrawn from the trial on November 3, 2008. A hemoglobin performed at the final study visit on November 3, 2008 was 11.7g/dl. The medical officer concurs that it is possible that this was related to the study drug.	Possible.
PN400-309-409-8254	52 year old White, Hispanic, female nonsmoker. Past medical history significant for osteoarthritis, obesity, chronic low back pain, left hip bursitis, ovarian cysts (s/p tubal ligation), and varicose veins. The patient was on no prior medications. Screening hemoglobin was 14.4g/dl on May 28, 2008. Study drug was dispensed on June 5, 2008. Follow-up hemoglobin on June 13, 2008 was 13.1g/dl and on July 7, 2008 12.0g/dl. Reportedly no source for blood loss could be found. On August 11, 2008 the patient took the last dose of study medication and was withdrawn from the trial. Hemoglobin at the final visit on August 11 was 12.6g/dl. It is interesting that an increase was seen in the hemoglobin on the same day that the study drug was withdrawn. This greatly decreases the likelihood that the drop in hemoglobin was study drug related but it does not preclude the possibility of a relationship.	Possible

Two study participants (0.17%) in the Vimovo withdrew due to abnormal liver function tests (ALT) (Patient PN400-307-035-6341 and PN400-304-467-4024). Normal ALT reference ranges were 0-55 U/L. Both patients had normal ALT at baseline with levels that increased to <2X ULN. After study drug was discontinued, the patients transaminases returned to normal. Another patient (PN400-302-499-2260) had a normal screening transaminase which then increased to >20X the ULN. However this patient was diagnosed with a duodenal ulcer and withdrawn from the study for that reason. The principal investigator attributed the increase initially to a lab error and later to a viral syndrome.

Two patients (0.17%) in the Vimovo group withdrew due to changes in BUN or creatinine (PN400-301-530-1499 and PN400-304-0499-4118). Patient PN400-301-530-1499 had an increase in creatinine from 0.9mg/dl at screening (normal range 0.6-1.1mg/dl) to 1.3 mg/dl at 3 months. This was assessed as possibly related to the study drug. Six days after the study drug was discontinued the creatinine level increased to 1.6 mg/dl. However at the early termination visit the value had returned to the normal range. Patient PN400-304-0499-4188 had a baseline BUN of 19mg/dl (normal range 6-23 mg/dl) which gradually increased over 9 months to a high of 38mg/dl. This was assessed as probably related to study drug. At the final visit 2 ½ months after study drug cessation, the value remained high at 33mg/dl.

Five (0.4%) study participants withdrew due to chest pain. Of note the terms chest pain, musculoskeletal chest pain, non-cardiac chest pain were combined under chest pain. One patient withdrew due to a myocardial infarction (PN400-301-506-1177) and upon review of the case report form, the medical officer could not reasonably attribute the myocardial infarction to the new drug.

Selected treatment emergent adverse events leading to discontinuations (including gastric and duodenal ulcers) from the Phase 3 studies in this clinical development program are outlined in the table below. Please note that all of the preferred terms for the Gastrointestinal, Musculoskeletal, Investigations, Cardiac, Vascular, and Renal SOCs are presented. Some preferred terms were combined as deemed appropriate by the medical officer.

Table 39 Summary of Treatment Emergent Adverse Events Leading to Trial Discontinuation by System Organ Class and Selected Preferred Terms for all Phase III Clinical Trials §

System Organ Class/ Preferred Term	Vimovo (N = 1166)	Naproxen (N = 426)	Celecoxib (N = 488)	Misoprostol (N = 11)	Placebo (N = 246)
Study Participant with Any Treatment Emergent Adverse Event Leading to Discontinuation	142 (12.2%)	173 (40.6%)	38 (7.8%)	6 (54.5%)	12 (4.9%)
Gastrointestinal Disorders	77 (6.6%)	154 (36.2%)	14 (2.9%)	4 (36.4%)	6 (2.4%)
Gastric Ulcer	26 (2.2%)	101 (23.7%)	0	1 (9.1%)	0
Duodenal Ulcer	3 (0.3%)	23 (5.4%)	1 (0.2%)	1 (9.1%)	0
Dyspepsia	8 (0.7%)	12 (2.8%)	4 (0.8%)	0	2 (0.8%)
Upper Abdominal Pain	9 (0.8%)	5 (1.2%)	3 (0.6%)	1 (9.1%)	0
Gastroesophageal reflux disease	3 (0.3%)	4 (0.9%)	4 (0.8%)	0	2 (0.8%)
Nausea	3 (0.3%)	2 (0.5%)	2 (0.4%)	1 (9.1%)	0
Diarrhea	5 (0.4%)	2 (0.5%)	0	0	0
Erosive gastritis	3 (0.3%)	4 (0.9%)	0	0	0
Abdominal pain	1 (<0.1%)	2 (0.5%)	0	0	0
Abdominal pain lower	3 (0.3%)	0	0	0	0
Constipation	3 (0.3%)	0	0	0	0
Abdominal discomfort	0	1 (0.2%)	1 (0.2%)	0	0
Erosive duodenitis	0	2 (0.5%)	0	0	0
Erosive esophagitis	1 (<0.1%)	1 (0.2%)	0	0	0
Esophageal ulcer	1 (<0.1%)	1 (0.2%)	0	0	0
Esophagitis	0	2 (0.5%)	0	0	0
Abdominal distension	0	1 (0.2%)	0	0	0
Abdominal tenderness	0	0	1 (0.2%)	0	0
Perforated appendicitis	1 (<0.1%)	0	0	0	0
Ischemic Colitis	1 (<0.1%)	0	0	0	0
Discolored Feces	1 (<0.1%)	0	0	0	0

System Organ Class/ Preferred Term	Vimovo (N = 1166)	Naproxen (N = 426)	Celecoxib (N = 488)	Misoprostol (N = 11)	Placebo (N = 246)
Gastrointestinal Disorders (continued)					
Gastrointestinal hemorrhage	1 (<0.1%)	0	0	0	0
Hematemesis	1 (<0.1%)	0	0	0	0
Hemorrhoids	1 (<0.1%)	0	0	0	0
Hyperchlorhydria	1 (<0.1%)	0	0	0	0
Irritable bowel syndrome	1 (<0.1%)	0	0	0	0
Stomach discomfort	0	0	0	0	1 (0.4%)
Vomiting	0	0	0	0	1 (0.4%)
Cardiac Disorders	5 (0.4%)	2(0.5%)	0	0	0
Coronary artery disease	1 (<0.1%)	1 (0.2%)	0	0	0
Palpitations	1 (<0.1%)	1 (0.2%)	0	0	0
Atrial flutter	1 (<0.1%)	0	0	0	0
Myocardial infarction	1 (<0.1%)	0	0	0	0
Supraventricular extrasystoles	1 (<0.1%)	0	0	0	0
Musculoskeletal and connective tissue disorders	19 (1.6%)	5 (1.2%)	10 (2.0%)	0	4 (1.6%)
Arthralgia	4 (0.3%)	1 (0.2%)	3 (0.6%)	0	3 (1.2%)
Back pain	3 (0.3%)	2 (0.5%)	2 (0.4%)	0	1 (0.4%)
Osteoarthritis	4 (0.3%)	1 (0.2%)	1 (0.2%)	0	0
Bursitis	1 (<0.1%)	0	2 (0.4%)	0	0
Arthritis	1 (<0.1%)	1 (0.2%)	0	0	0
Intervertebral disc protrusion	1 (<0.1%)	0	1 (0.2%)	0	0
Musculoskeletal pain	1 (<0.1%)	0	1 (0.2%)	0	0
Chondrocalcinosis pyrophosphate	1 (<0.1%)	0	0	0	0
Exostosis	1 (<0.1%)	0	0	0	0
Joint swelling	1 (<0.1%)	0	0	0	0

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System Organ Class/ Preferred Term	Vimovo (N = 1166)	Naproxen (N = 426)	Celecoxib (N = 488)	Misoprostol (N = 11)	Placebo (N = 246)
Investigations	11 (0.9%)	0	3 (0.6%)	0	0
Increased blood pressure	3 (0.3%)	0	2 (0.4%)	0	0
Decreased hemoglobin/hemoglobin abnormal/anemia	4 (0.3%)	1(0.2%)	1 (0.2%)	0	0
Blood creatinine increased	1(<0.1%)	0	0	0	0
Blood urea increased	1 (<0.1%)	0	0	0	0
Abnormal liver functions	2 (0.17)	0	0	0	0
General disorders and administration site conditions	9 (0.8%)	0	4 (0.8%)	0	0
Chest pain/Non-cardiac chest pain/Musculoskeletal chest pain	5 (0.4%)	2 (0.4%)	0	0	0
Peripheral edema/swelling	4 (0.3%)	0	1 (0.2%)	0	0
Fatigue	0	0	1 (0.2%)	0	0
Nervous system disorders	7 (0.6%)	1 (0.2%)	1 (0.2%)	1 (9.1%)	0
Headache	1 (<0.1%)	1 (0.2%)	1 (0.2%)	0	0
Dizziness	2 (0.2%)	0	0	0	0
Carotid artery stenosis	1 (<0.1%)	0	0	0	0
Migraine	0	0	0	1 (9.1%)	0
Sciatica	1 (<0.1%)	0	0	0	0
Syncope	1 (<0.1%)	0	0	0	0
Transient ischemic attack	2 (0.2%)	0	0	0	0
Skin and subcutaneous tissue disorders	6 (0.5%)	1 (0.2%)	1 (0.2%)	0	0
Pruritis/Pruritis allergic/pruritis generalized	3 (0.3%)	0	1 (0.2%)	0	0
Rash/Rash generalized	3 (0.3%)	0	0	0	0
Diabetic ulcer	0	1 (0.2%)	0	0	0

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System Organ Class/ Preferred Term	Vimovo (N = 1166)	Naproxen (N = 426)	Celecoxib (N = 488)	Misoprostol (N = 11)	Placebo (N = 246)
Urticaria	1 (<0.1%)	0	0	0	0
Infections and infestations	3 (0.3%)	3 (0.7%)	1 (0.2%)	0	0
Herpes zoster	1 (<0.1%)	0	1 (0.2%)	0	0
Bronchitis	0	1 (0.2%)	0	0	0
Diverticulitis	0	1 (0.2%)	0	0	0
Pneumonia	1 (<0.1%)	0	0	0	0
Post procedural infection	0	1 (0.2%)	0	0	0
Staphylococcal infection	1 (<0.1%)	0	0	0	0
Injury, poisoning and procedural complications	2 (0.2%)	2 (0.5%)	1 (0.2%)	0	0
Fracture/hip fracture/upper limb fracture	1 (<0.1%)	2 (0.5%)	0	0	0
Incisional hernia	1 (<0.1%)	0	0	0	0
Vascular disorders	1 (<0.1%)	2 (0.5%)	1 (0.2%)	0	1 (0.4%)
Hypertension	1 (<0.1%)	2 (0.5%)	1 (0.2%)	0	1 (0.4%)
Respiratory, thoracic, and mediastinal disorders	1 (<0.1%)	1 (0.2%)	0	0	1 (0.4%)
Diaphragmatic disorder	0	0	0	0	1 (0.4%)
Dyspnea	1 (<0.1%)	0	0	0	0
Hypercapnia	0	1 (0.2%)	0	0	0
Immune system disorders	0	0	2 (0.4%)	0	0
Anaphylactic reaction	0	0	1 (0.2%)	0	0
Drug hypersensitivity	0	0	1 (0.2%)	0	0

System Organ Class/ Preferred Term	Vimovo (N = 1166)	Naproxen (N = 426)	Celecoxib (N = 488)	Misoprostol (N = 11)	Placebo (N = 246)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.2%)	0	0	0	0
Breast cancer	1 (<0.1%)	0	0	0	0
Thyroid cancer	1 (<0.1%)	0	0	0	0
Ear and labyrinth disorders	1 (<0.1%)	0	0	0	0
Tinnitus	1 (<0.1%)	0	0	0	0
Hepatobiliary disorders	1 (<0.1%)	0	0	0	0
Hepatomegaly	1 (<0.1%)	0	0	0	0
Psychiatric disorders	0	1 (0.2%)	0	0	0
Depression	0	1 (0.2%)	0	0	0
Renal and urinary disorders	1 (<0.1%)	0	0	0	0
Nephrolithiasis	1 (<0.1%)	0	0	0	0

Reviewers Table. Modified from Sponsors Table 5.3.5.3.2.27 Integrated Summary of Safety p81/2911 and Table S1.5 p 375/2911

§ Includes Trial PN400-303 which was terminated early due to poor enrollment.

Analysis of treatment emergent adverse events leading to withdrawal by age is consistent with the general pattern of discontinuation. Withdrawals did not increase with increases in age in the Vimovo group. The following table provides information on treatment emergent adverse events leading to discontinuation by age subgroups in all Phase III studies for Vimovo. The medical officer chose to highlight SOCs and preferred terms that were relevant for the particular drug classes in order to determine if there any safety signals.

Table 40 Summary of Selected Treatment Emergent Adverse Events Leading to Discontinuation by Age Subgroups in all Phase III Trials for Vimovo

SOC/ Preferred Term	Age Subgroups					
	<60 yrs (n = 542)	≥60 yrs (n = 642)	< 65 yrs (n = 776)	≥65 yrs (n = 390)	< 75 yrs (n = 1080)	≥75 yrs (n = 86)
Overall	74 (13.7%)	68 (10.9%)	100 (12.9%)	42 (10.9%)	129 (11.9%)	13 (15.1%)
Gastrointestinal	44 (8.1%)	33 (5.3%)	60 (7.7%)	17 (4.4%)	73 (6.8%)	4 (4.7%)
Gastric ulcer	19 (3.5%)	7 (1.1%)	24 (3.1%)	2 (0.5%)	26 (2.4%)	0
Duodenal ulcer	2 (0.4%)	1 (0.2%)	3 (0.4%)	0	3 (0.3%)	0
Dyspepsia	6 (1.1%)	2 (0.3%)	6 (0.8%)	2 (0.5%)	8 (0.7%)	0
Nausea	2 (0.4%)	1 (0.2%)	3 (0.4%)	0	3 (0.3%)	0
Diarrhea	2 (0.4%)	3 (0.5%)	3 (0.4%)	2 (0.5%)	4 (0.4%)	1 (1.2%)
Musculoskeletal	8 (1.5%)	11 (1.8%)	11 (1.4%)	8 (2.1%)	18 (1.7%)	1 (1.2%)
Arthralgia	1 (0.2%)	3 (0.5%)	1 (0.1%)	3 (0.8%)	4 (0.4%)	0
Backpain	1 (0.2%)	2 (0.3%)	1 (0.1%)	2 (0.5%)	3 (0.3%)	0
Investigations	3 (0.6%)	7 (1.1%)	6 (0.8%)	4 (1.0%)	9 (0.8%)	1 (1.2%)
Increased blood pressure	0	3 (0.5%)	1 (0.1%)	2 (0.5%)	3 (0.3%)	0
Decreased hemoglobin	1 (0.2%)	1 (0.2%)	3 (0.4%)	0	3 (0.3%)	0
Increased creatinine	0	1 (0.2%)	1 (0.1%)	0	1 (<0.1%)	0
Increased BUN	0	1 (0.2%)	0	1 (0.3%)	1 (<0.1%)	0
Abnormal transaminases	0	1 (0.2%)	1 (0.1%)	0	1 (<0.1%)	1 (1.2%)
General Disorders	5 (0.9%)	3 (0.5%)	5 (0.6%)	3 (0.8%)	6 (0.6%)	2 (2.3%)
Peripheral edema	2 (0.4%)	2 (0.3%)	2 (0.3%)	2 (0.5%)	3 (0.3%)	1 (1.2%)
Chest pain	3 (0.6%)	1 (0.2%)	1 (0.1%)	1 (0.3%)	3 (0.3%)	1 (1.2%)
Cardiac	2 (0.4%)	3 (0.5%)	3 (0.4%)	2 (0.5%)	4 (0.4%)	1 (1.2%)
Coronary Artery Disease	1 (0.2%)	0	1 (0.1%)	0	1 (<0.1%)	0
Palpitations	0	1 (0.2%)	0	1 (0.3%)	0	0
Atrial Flutter	0	1 (0.2%)	1 (0.1%)	0	1 (<0.1%)	0
Myocardial Infarction	0	1 (0.2%)	0	1 (0.3%)	1 (<0.1%)	1 (1.2%)
Ventricular extrasystoles	1 (0.2%)	0	1 (0.1%)	0	1 (<0.1%)	1 (1.2%)
Vascular	0	1 (0.2%)	0	1 (0.8%)	1 (<0.1%)	0
Hypertension	0	1 (0.2%)	0	1 (0.8%)	1 (<0.1%)	0

Age Subgroups						
	<60 yrs (n = 542)	≥60 yrs (n = 642)	< 65 yrs (n = 776)	≥65 yrs (n = 390)	< 75 yrs (n = 1080)	≥75 yrs (n = 86)
SOC/ Preferred Term						
Blood/Lymphatic Anemia	1 (0.2%) 1 (0.2%)	0 0	1 (0.1%) 1 (0.1%)	0 0	1 (<0.1%) 1 (<0.1%)	0 0
Infections and infestations Pneumonia	1 (0.2%) 0	1 (0.3%) 1 (0.2%)	1 (0.1%) 0	2 (0.5%) 1 (0.3%)	2 (0.2%) 0	1 (1.2%) 1 (1.2%)
Injury, poisoning, and procedural complications Fractures	0 0	2 (0.3%) 1 (0.2%)	0 0	2 (0.5%) 1 (0.3%)	1 (<0.1%) 1 (<0.1%)	0 0
Renal Nephrolithiasis	1 (0.2%) 1 (0.2%)	0 0	1 (0.1%) 1 (0.1%)	0 0	1 (<0.1%) 1 (<0.1%)	0 0

Reviewers Table Adapted from Sponsors Table 5.3.5.3.2.28 p82/2911; table S1.6; Table S1.7; Table S1.8 Integrated Summary Safety

The number of discontinuations also did not increase with increased duration of exposure. The majority of the events of the events leading to discontinuation occurred within the first 3 months of treatment. There were no specific correlations between duration of exposure and withdrawals for cardiac events, renal events, changes in blood pressure, changes in transaminases, changes in hemoglobin, or peripheral edema. The following table summarizes adverse events leading to discontinuation by time of onset for the SOC and selected preferred terms that the medical reviewer believed were most relevant to the therapeutic drug classes. Because there was some splitting present, the medical officer combined preferred terms as deemed medically appropriate.

Table 41 SOC and Selected Preferred Terms of Adverse Events Leading to Discontinuation of Vimovo by AE Day of Onset (Expanded Safety Population)

SOC/ Preferred Term	Study Day of Event Onset					Overall
	1-14 Days	15-30 Days	31-90 Days	91-180 Days	>180 Days	
All Adverse Events	29	32	42	30	11	144
Gastrointestinal disorders overall	14	18	20	17	5	76
Gastric ulcer	0	6	4	9	5	24
Abdominal pain	4	2	3	3	0	12
Dyspepsia	4	1	2	1	0	8
Diarrhea	3	1	1	0	0	5
Constipation	1	0	1	1	0	3
Duodenal ulcer	0	1	2	0	0	3
GERD	1	0	1	0	0	2
Nausea	1	1	1	0	0	3
Hyperchlorhydria	0	0	1	0	0	1
Esophageal Ulcer	0	0	0	1	0	1
Gastrointestinal hemorrhage	0	1	0	0	0	1
Hematemesis	0	0	1	0	0	1
Musculoskeletal overall	2	5	5	3	4	19
Athralgia/pain	1	1	4	2	1	9
Joint swelling	1	0	0	0	1	2
Osteoarthritis	0	2	0	1	1	4
Investigations overall	3	1	3	2	1	10
Increased blood pressure	2	0	1	0	0	3
Hemoglobin decreased	1	0	2	0	0	3
Increased BUN	0	0	0	0	1	1
Increased creatinine	0	0	0	1	0	1
Abnormal liver function tests	0	1	0	1	0	2
General Disorders overall	3	1	3	0	1	8
Peripheral edema	1	1	2	0	0	4
Chest pain/Noncardiac chest pain	2	0	1	0	1	4
Skin/subcutaneous tissue disorder	2	2	4	0	0	8

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SOC/ Preferred Term	Study Day of Event Onset					Overall
	1-14 Days	15-30 Days	31-90 Days	91-180 Days	>180 Days	
Cardiac Disorders overall	1	1	1	2	0	5
Atrial flutter	0	0	0	1	0	1
Coronary artery disease	0	0	1	0	0	1
Myocardial infarction	0	0	0	1	0	1
Palpitations	1	0	0	0	0	1
Supraventricular extrasystoles	0	1	0	0	0	1
Infections and infestations overall	0	1	1	1	0	3
Pneumonia	0	0	1	0	0	1
Injury/poison/procedural complications overall	1	0	1	0	0	2
Fractures	1	0	0	0	0	1
Blood and lymphatic system disorders overall	0	0	1	0	0	1
Anemia	0	0	1	0	0	1
Renal overall	0	0	1	0	0	1
Nephrolithiasis	0	0	1	0	0	1
Hepatobiliary disorders overall	0	1	0	0	0	1
Hepatomegaly	0	1	0	0	0	1
Vascular Disorders overall	0	0	1	0	0	1
Hypertension	0	0	1	0	0	1
Neoplasms overall	0	0	0	2	0	2
Breast Cancer	0	0	0	1	0	1
Thyroid Cancer	0	0	0	1	0	1

Reviewers Table Adapted from Sponsor's Table S4.34 p2234/2911 Integrated Summary of Safety. For this Table the counts are events, not study participants. Events are summarized in decreasing order based on the overall occurrence rate. The Expanded Safety Population does not include patients from Trial PN400-303 which was terminated early

7.3.4 Significant Adverse Events

Please see section 7.3.5 below for additional information.

ICH E3 defines “other significant adverse events” as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of a test drug, dose reduction or significant additional concomitant therapy other than those reported as serious adverse events.

The medical reviewer chose to examine the Expanded Safety Population for the Significant Adverse Events analysis. This population included all patients from the Phase III trials except for trial PN400-303 which was terminated early.

Of the 1157 patients in the Expanded Safety Population, 85 (7.3%) developed a severe adverse event. Most of these (40 or 3.5%) were in the SOC of Gastrointestinal disorders. Again the most commonly reported preferred term was dyspepsia. There were 32 patients (2.8%) who reported adverse events consistent with cardiorenal peripheral edema. All of these were assessed as either mild or moderate in severity. However, of these 32 patients, 5 withdrew (patients PN400-302-603-2712, PN400-304-502-4042, PN400-307-007-6102, PN400-309-431-8043, PN400-304-275-4162). Another 5 patients (PN400-301-537-1696, PN400-301-491-1263, PN400-304-479-4206, PN400-304-564-4176, PN400-307-035-6343) were prescribed diuretics as a result of the edema.

7.3.5 Submission Specific Primary Safety Concerns

The medical officer used Hy’s Law to assess for the potential of Vimovo to cause severe liver injury. There were no patients in any of the Phase 3 studies meeting strick Hy’s law criteria (elevated ALT greater than three times the upper limit of normal (ULN) with concurrent increase in bilirubin greater than two times the upper limit of normal and alkaline phosphatase less than two times the upper limit of normal).

A potential for severe drug induced liver injury is signaled when there is an excess of aminotransferase elevations greater than or equal to 3 times the upper limit of normal (3XULN) in the treatment group compared to the control group. However, aminotransferase elevations greater than or equal to 3 times the upper limit of normal are relatively common. At present, there are no good data to predict how large of an excess in the incidence of aminotransferase elevations in the treatment group relative to the control group is indicative of an increased risk for drug induced liver injury.

It is important to note that the sponsor performed analyses using both normal ranges and extended ranges for hematology and chemistry values. These normal values are presented in the table below.

Table 42 Listing of Normal Range and Extended Normal Range Laboratory Test Values for Liver Function Tests All Phase 3 Trials

Test	Gender	Age Range	Normal Reference Range	Extended Reference Range	Units
Alkaline Phosphatase	Females	All	37 – 147	0 – 330	U/L
	Males	All	37 – 147	0 – 330	U/L
ALT	Females	All	0 – 55	0 – 90	U/L
	Males	All	0 -- 55	0 – 90	U/L
AST	Females	All	0 – 45	0 – 90	U/L
	Males	All	0 – 45	0 – 90	U/L
Total Bilirubin	Females	All	0.3 – 1.5	0 – 1.75	mg/dl
	Males	All	0.3 – 1.5	0 – 1.75	mg/dl

The following table provides an analysis of the incidence rates of clinically relevant hepatic related chemistry changes comparing the treatment group from the Expanded Safety Population.

Table 43 Clinically Relevant Hepatic Transaminases from the Expanded Safety Population

Assessment	Vimovo N = 1157	Naproxen N = 426	Celecoxib N = 488	Placebo N = 246
Total Study Participants with ALT Changes (normal 0-55 U/L)	3 (0.26%)	2 (0.47%)	0	1 (0.41%)
ALT ≥ 3X ULN	3 (0.26%)	2 (0.47%)	0	1 (0.41%)
ALT ≥ 5X ULN	2 (0.17%)	0	0	0
ALT ≥ 10X ULN	1 (0.09%)	0	0	0
ALT ≥ 20X ULN	1 (0.09%)	0	0	0
Total Study Participants with AST Changes (Normal 0-45 U/L)	5 (0.43%)	0	0	1 (0.41%)
AST ≥ 3X ULN	5 (0.43%)	0	0	1 (0.41%)
AST ≥ 5X ULN	2 (0.17%)	0	0	0
AST ≥ 10X ULN	1 (0.09%)	0	0	0
AST ≥ 20X ULN	1 (0.09%)	0	0	0
Total Study Participants with bilirubin changes	4 (0.35%)	0	2 (0.41%)	3 (1.2%)
Total bilirubin ≥ 1.5X ULN	1 (0.09%)	0	0	1 (0.41%)
Total bilirubin ≥ 2.0X ULN	1 (0.09%)	0	0	1 (0.41%)
Total Study Participants with Alkaline Phosphate changes	7 (0.61%)	1 (0.23%)	0	0
Alk Phos ≥ 1.5X ULN	7 (0.61%)	1 (0.23%)	0	0
Alk Phos ≥ 3.0X ULN	1 (0.09%)	0	0	

Sponsor's Table 5.3.5.3.2.37 Integrated Summary of Safety p112/2911.

In the current submission the number of patients with abnormal liver function test was greater in the Vimovo group relative to the other control groups. However the overall occurrence rate was less than 1%. For the control groups combined (Naproxen, Celecoxib, and Placebo) there was 1 (0.09%) patient that had concurrent AST and ALT elevations greater than or equal to 3 times the ULN.

In the current labeling for Naproxen, it states that borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs. These laboratory

abnormalities may progress, remain essentially unchanged, or may be transient with continued therapy. There were 3 (0.26%) patients that had concurrent elevations in ALT and AST greater than or equal to 3 times the upper limit of normal. There were two additional patients (0.17%) that had solely AST greater than or equal to 3 times the upper limit of normal (ULN) in the Vimovo group. One patient (PN400-302-499-2260) had both normal ALT and AST at baseline and experienced elevations in both parameters to $\geq 20X$ ULN (ALT 2948 U/L and AST 4046 U/L). The principal investigator felt this was unrelated to the study drug. The patient was withdrawn from the study due to a duodenal ulcer. However, the incidence warrants further investigation.

Per report, patient PN400-302-499-2260 had been under the care of the principal investigator for several years prior to study entry. Reportedly, this was a 47 year old male with a past medical history significant for smoking, hypertension, dyslipidemia, gastric ulcer, Barrett's esophagus, insomnia, and anxiety. The patient had no prior history of gallbladder or previous liver disease. Ongoing concomitant medications included aspirin, atenolol, clonazepam, trazodone, fenofibrate and valsartan. Thirty three days after starting study drug, the patient returned to clinic for a scheduled endoscopy. Per report, study laboratory tests were drawn in the morning and the patient underwent endoscopy in the afternoon, where duodenal ulcers were detected causing the patient to be withdrawn from the study as per protocol. Allegedly at the time of the visit, the patient also reported several adverse events including nausea, bronchospasm, and cough. The patient had been taking epinephrine inhalers at home for these symptoms. It is also stated in the report that the patient was given a 2cc IM injection of dexamethasone but it does not state by whom and when. The principal investigator attributed the nausea to the presence of the peptic ulcer that was found on endoscopy. It is interesting that the patient was still able to undergo the procedure despite his reported physical state. Notwithstanding, when the laboratory results returned later, the patient had a serum ALT of 2948 U/L and an AST of 4046 U/L with a total bilirubin of 0.7mg/dL and alkaline phosphatase of 83U/L. All other laboratory assessments were normal. The principal investigator did not report the increases in ALT and AST as an adverse event and initially attributed the results to a lab error. There is no mention of plans to repeat to lab results. Reportedly the patient was scheduled for end of study assessments the following day, March 13, but cancelled due to flu-like symptoms. Per report he patient returned for a follow-up visit approximately 1 month later at which time he was reported to be recovering from a cold and feeling better. He also complained of knee pain and decreased memory. There was no report of jaundice. The patient was given samples of rabeprazole for the management of his duodenal ulcer and Vicodin for his knee pain. Laboratory results from the April 9, 2008, final study visit included a normal AST (39U/L), slightly elevated ALT (83 U/L), an elevated total bilirubin of 3.2 mg/dl and an alkaline phosphatase of 249 U/L. Another follow-up visit occurred May 13, 2008. At that time, the patient reported severe heartburn and was prescribed esomeprazole. Allegedly the patient had several follow-up visits with no reports of hepatic adverse events. Laboratory evaluations were performed in January, February, and March 2009. These tests reported normal CBCs, normal ASTs, one abnormal ALT (61 U/L, normal range 0 -48 U/L), normal total bilirubins and normal alkaline

phosphatases. The investigator's assessment initially was that the elevated ALT and AST were not related to study drug. The investigator attributed the increases in hepatic transaminases to a concurrent viral syndrome. The medical reviewer finds the course and timing of events somewhat disturbing. Naproxen, a component of the Vimovo tablet, is known to cause abnormal liver function tests and hepatitis (in some cases fatal). Given the degree of elevation and the fact that the patient had recently started a study medication, it is concerning that this was attributed only to lab error. Additionally this degree of elevation is not common with simple "cold or flu-like" viral illnesses. The persistently elevated ALT, total bilirubin, and alkaline phosphatase one month after study cessation suggests some type of hepatic insult occurred and it can not be ruled out that this was possibly study drug related.

Table 44 Summary of Hepatic Function Tests Patient PN400-302-499-2260

Hepatic function test (Normal ranges)	ALT (0 – 55 U/L)	AST (0 – 45 U/L)	Total bilirubin (0.3 – 1.5 mg/dl)	Alkaline Phosphatase (37 – 147 U/L)
On Study				
01/24/08 (Baseline)	20	20	0.2	54
03/15/2008 (1 month) Withdrawn	2948	4046	0.7	83
04/09/2008 (End of study Visit)	83	39	3.2	249
Post-Study				
01/05/2009	23	20	0.6	75
01/26/2009	30	25	0.3	80
02/17/2009	61	27	0.2	144
03/13/2009	15	18	0.3	142

Patient PN400-301-589-1613 also experienced ALT and AST elevations $\geq 5X$ ULN. However, this patient had elevated baseline values (ALT 83 U/L and AST 65 U/L). This patient was a 55 year old white female with an extensive past medical history including hypoglycemia, hyperlipidemia, myopia, hyperopia, astigmatism, GERD, gastritis, intermittent constipation, chronic low back pain, cervical disc disease, cervical neuralgia, osteoarthritis of the knee, fibromyalgia, fatigue, anxiety, insomnia, estrogen deficiency, decreased libido, emphysema, and asthma. Patient medications included estrogen, methyl-testosterone and salmeterol fluticasone propionate inhaler.

Interestingly, increases again were observed around the 1-month interval (ALT 373 U/L and AST 336 U/L). In response to these values, the labs were repeated 10 days later (ALT 94 U/L and AST 67 U/L) and again 7 days thereafter (ALT 37U/L and AST 34 U/L). The patient was withdrawn from the study because of a scheduled surgery but was able to complete the final visit. Labs at the final visit were normal (22 U/L ALT and 23 U/L AST). The investigator felt that this was possibly related to the study medication and the medical reviewer concurs with this finding.

Using the normal reference values, the sponsor report ALT shifted from low or normal to high in 4.9% of study participants and ALT shifted from low or normal to high in 4.4% of study participants taking Vimovo in all phase 3 trials. Using the expanded normal reference ranges, 0.9 % of study participants had shifts in ALT and 0.7% had shifts in AST from low or normal to high. Again the medical officer noted that most of these shifts in transaminases occurred around 1 month after the initiation of study medication. Two patients experienced mild elevations in AST that occurred following approximately 9 months of therapy.

Increases in total bilirubin occurred in 4 study participants who took Vimovo, however only patient (PN400-302-499-2260) experienced an increase in total bilirubin $\geq 1.5X$ or $2X$ upper limit of normal. This rise in bilirubin was noted 1 month after the marked elevations in ALT and AST. By that time study medication has ceased. However, again we can not rule out the possibility of a possible drug induced liver injury.

Seven patients who took Vimovo experienced an elevation in alkaline phosphatase that was $1.5X \geq ULN$. One patient (PN400-307-035-6341) experienced increase in alkaline phosphatase $\geq 3X ULN$ and an increase in total bilirubin (2.2 mg/dl) on the same day.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Per the sponsor, adverse events were sought by non-directive questioning at each visit after the patient had an opportunity to spontaneously mention any problems. Adverse events were also detected through physical examination, laboratory tests or other assessments. In addition to recording spontaneously reported heartburn and dyspeptic symptoms on eCRFs, heartburn and dyspepsia were addressed using responses on the Overall Treatment Evaluation Dyspepsia rating and the Severity of Dyspepsia Assessment scales. In studies PN400-307 and PN400-309 a modified version of the Severity of Dyspepsia Assessment Scale was obtained.

Using the adverse events analysis dataset files for the pivotal studies PN400-301 and PN400-302 provided by the applicant in the June 30, 2009 submission, the medical

reviewer verified the counts for the common treatment emergent adverse events in the primary safety population using JMP statistical software. These are the adverse events that will be included in the labeling.

Table 45 Common Treatment Emergent Adverse Events, Including Gastric and Duodenal Ulcer, Occurring \geq 2% in the Primary Safety Primary

Preferred Terms	Vimovo n = 428	EC Naproxen n = 426
Erosive Gastritis	83 (19.4%)	162 (38.0%)
Dyspepsia	77 (18.0%)	114 (26.8%)
Diarrhea	26 (6.1%)	22 (5.2%)
Upper Abdominal Pain	24 (5.6%)	37 (8.7%)
Gastric ulcer	24 (5.6%)	101 (23.7%)
Nausea	22 (5.1%)	21 (4.9%)
Upper respiratory tract	21 (4.9%)	16 (3.8%)
Hiatus hernia	18 (4.2%)	25 (5.9%)
Abdominal distension	16 (3.7%)	16 (3.8%)
Flatulence	16 (3.7%)	13 (3.1%)
Esophagitis	15 (3.5%)	32 (7.5%)
Constipation	11 (2.6%)	12 (2.8%)
Headache	11 (2.6%)	6 (1.4%)
Abdominal pain	10 (2.3%)	7 (1.6%)
Bronchitis	10 (2.3%)	8 (1.9%)
Cough	10 (2.3%)	11 (2.6%)
Urinary tract infection	10 (2.3%)	6 (1.4%)
Lower Abdominal Pain	9 (2.1%)	11 (2.6%)
Dysgeusia	9 (2.1%)	6 (1.4%)
Erosive duodenitis	9 (2.1%)	50 (11.7%)
Sinusitis	8 (1.9%)	9 (2.1%)
Duodenitis	6 (1.4%)	31 (7.3%)
Arthralgia	5 (1.2%)	10 (2.3%)
Gastritis hemorrhagic	5 (1.2%)	9 (2.1%)
Gastroesophageal reflux	4 (0.9%)	15 (3.5%)
Nasopharyngitis	4 (0.9%)	10 (2.3%)
Duodenal ulcer	3 (0.7%)	23 (5.4%)
Erosive esophagitis	2 (0.5%)	24 (5.6%)

Reviewer's Table recreated from Sponsor's Table 5.3.5.3.2.12 p35/2911 Integrated Summary of Safety

Overall 78.3% of patients taking Vimovo and 87.6% of patients taking Naproxen reported an adverse event in the primary safety population. The majority of treatment emergent adverse events by preferred term in greater than or equal to 2% of study participants occurred under the SOC Gastrointestinal disorders. Erosive gastritis was found in 19.4% of the Vimovo arm and 38.0% of the Naproxen arm. Dyspepsia was found in 18.0% of the Vimovo arm and 26.8% of the Naproxen arm. The percentage of

patients that experienced nausea was comparable between the two groups (5.1% in the Vimovo group, 4.9% in the Naproxen group). More patients in the Vimovo group relative to the Naproxen group experienced gastritis (17.1% vs. 14.1%), upper respiratory infection (4.9% vs. 3.8%), headache (2.6% vs. 1.4%), abdominal pain (2.3% vs. 1.6%), bronchitis (2.3% vs. 1.9%), and urinary tract infection (2.3% vs. 1.4%). The higher incidence of upper respiratory infections and slight increase in bronchitis were noted because some studies have indicated that long term use of proton pump inhibitors may be associated with an increase incidence of upper respiratory infections and pneumonia.

It is interesting that the sponsor chose $\geq 2\%$ of the primary safety population as the threshold for adverse events. When the reviewer lowered the threshold to $\geq 1\%$ of the population, the incidence gastric polyps was higher in the Vimovo group (1.2%) relative to the Naproxen (0.2%). This is not surprising because since 1992 there have been reports of proton pump inhibitors being associated with fundic-gland type gastric polyps.¹⁴ Additionally the incidence of muscle spasms (1.9% vs. 0.2%), musculoskeletal pain (1.4% vs. 0.7%), rash (1.6% vs. 0.5%) and anemia (1.4% vs. 0.9%) was also higher in the Vimovo group relative to the Naproxen group. When the medical reviewer combined the preferred terms “alanine aminotransferase increased”, “aspartate aminotransferase increased”, “liver function test abnormal” and “hepatic enzyme increased” into one term “abnormal liver function test”, the incidence was 1.4% in the Vimovo group and 0.7% in the Naproxen group. (It is important to note that the denominators used for these calculations were $n = 428$ for Vimovo and $n = 426$ for Naproxen). It is also important to note that with the lowered threshold, there were still no safety signals detected in the primary safety population from the Cardiac, Vascular, or Renal and Urinary Disorders SOCs or preferred terms within these SOCs.

There were no cardiovascular treatment emergent adverse events in the patients who entered the primary safety population with no prior history of cardiovascular disease. Of those that had a history of cardiovascular disease, 2.4% in the Vimovo arm and 2.2% in the Naproxen arm developed a cardiac treatment emergent adverse event. One patient with a prior cardiovascular history (0.4%) experienced a myocardial infarction in the Vimovo group. There were no myocardial infarctions reported in the Naproxen group.

The sponsor selected cardiovascular events to compare between treatment groups in the primary safety population regardless of cardiovascular history. These included hypertension, increased blood pressure, unstable angina, atrial flutter, coronary artery disease, myocardial infarction, syncope, ventricular tachycardia, angina pectoris, bradycardia, cardiac failure, and congestive cardiac failure. The overall incidence of these selected cardiovascular adverse events was similar between the two treatment groups (2.3% Naproxen and 2.6% Vimovo). Selected cardiovascular events other than hypertension occurred in 0.7% of study participants taking Vimovo and 0.9% of those taking Naproxen. There was some minor splitting of terms. However, when you combined the terms (i.e. hypertension and increased blood pressure), there was still no difference observed between the treatment groups. In the case of the aforementioned

increased blood pressure, 1.6% of Vimovo patients and 1.6% of Naproxen patients had an increase in blood pressure. All other preferred terms were seen in less than 1% in either treatment group.

Treatment emergent adverse events reported in those study participants of the primary safety population with and without concomitant low dose aspirin use at study entry were also analyzed. The percentage of patients who reported an adverse event was not substantially higher in the group with concomitant low-dose aspirin (79.8%) relative to the group without concomitant low-dose aspirin use (77.8%). The lack of effect of concurrent low-dose aspirin use was also seen the Naproxen arm where 85.3% of those with concomitant aspirin use reported an adverse event and 88.3% of those without concomitant low-dose aspirin use reported an adverse event.

Interestingly, the use of low-dose aspirin did not appear to substantially affect the rates of adverse events reported in the SOC Gastrointestinal Disorders in either the Vimovo or the Naproxen arms. Concurrent use of low-dose aspirin is a known risk factor for NSAID induced GI toxicity. Of those that took Vimovo and low-dose aspirin 65.7% reported an adverse event from the GI SOC. Of those who took Vimovo but did not have low-dose aspirin use 62.9% reported an adverse event. For the Naproxen arm the adverse event rate was 81.4% and 79.9% with and without low dose aspirin use respectively. The most commonly reported preferred terms were dyspepsia and erosive esophagitis in both groups of patients with and without low-dose aspirin use. Surprisingly, there were no substantial differences in the incidence of duodenal ulcer, erosive gastritis, or esophagitis in patients who took low dose aspirin compared to those who did not take low-dose aspirin. Interestingly fewer study participants taking Vimovo and low-dose aspirin developed a gastric ulcer (3.0%) than those taking Vimovo without low-dose aspirin (6.4%). This is exactly opposite of what would normally be expected. The same pattern was also seen in the Naproxen arm, where the incidence of gastric ulcers was 22.2% in patients taking Naproxen without low-dose aspirin and the incidence of gastric ulcers was 28.4% in those taking Naproxen with low-dose aspirin.

There were no significant differences in the incidence and distribution of the treatment emergent adverse events from Vimovo by race. There were some slight differences in the reporting of treatment emergent adverse events by ethnicity. Hispanics taking Vimovo reported slightly more GI and Nervous System adverse events. There were no substantial differences between males and females in the frequency or distribution of adverse events. More females in the Vimovo group (3.9%) reported “headaches” than females in the EC naproxen group (1.4%). Per the sponsor, with the exception of the Nervous System Disorders, the number of treatment emergent adverse events associated with Vimovo also did not appear to increase with age. The medical officer also could not detect relationship pattern between increasing age and adverse events. More patients over and under the age of 60 in the Vimovo group (6.9% and 10.4% respectively) relative to the Naproxen group (4.1% and 7.7%) reported an adverse event in the SOC Nervous System Disorders. Again this was driven by a higher rate of headaches in the Vimovo group. The following table provides the treatment emergent

adverse events by decade of age for Primary Safety Population of selected SOC and preferred terms. SOC and preferred terms were included in this table were based upon the therapeutic drug class. There was very minor splitting of some preferred terms.

Table 46 Selected Treatment Emergent Adverse Events By Age (in Decade) Primary Safety Population

System Organ Class/ Preferred Term	Age < 50 years		50 – 59 years		60 – 69 years		> 70 years	
	Vimovo N = 14	Naproxen n = 9	Vimovo n = 202	Naproxen n = 208	Vimovo n = 157	Naproxen n = 142	Vimovo n = 55	Naproxen n = 67
Study Participant with ANY Adverse Event	12 (85.7%)	8 (88.9%)	163 (80.7%)	186 (89.4%)	119 (75.8%)	124 (87.3%)	41 (74.5%)	55 (82.1%)
Gastrointestinal Disorders overall	9 (64.3%)	8 (88.9%)	137 (67.8%)	170 (81.7%)	99 (63.1%)	115 (81.0%)	27 (49.1%)	49 (73.1%)
Dyspepsia	3 (21.4%)	5 (55.6%)	43 (21.3%)	58 (27.9%)	23 (14.6%)	38 (26.8%)		13 (19.4%)
Gastric ulcer	3 (21.4%)	2 (22.2%)	15 (7.4%)	44 (21.2%)	6 (3.8%)	40 (28.2%)	8 (14.5%)	15 (22.4%)
Erosive gastritis	3 (21.4%)	2 (22.2%)	44 (21.8%)	80 (38.5%)	29 (18.5%)	64 (45.1%)	0	16 (23.9%)
Nausea	2 (14.3%)	1 (11.1%)	9 (4.5%)	5 (2.4%)	4 (2.5%)	13 (9.2%)	7 (12.7%)	2 (3.0%)
Duodenal ulcer	2 (7.1%)	1 (11.1%)	1 (0.5%)	13 (6.3%)	1 (0.6%)	4 (2.8%)	7 (12.7%)	5 (7.5%)
Gastritis	1 (7.1%)	0	36 (17.8%)	34 (16.3%)	31 (19.7%)	16 (11.3%)	0	10 (14.9%)
Abdominal discomfort	0	1 (11.1%)	2 (1.0%)	4 (1.9%)	3 (1.9%)	1(0.7%)	5 (9.1%)	2 (3.0%)
Abdominal pain upper	0	1 (11.1%)	15 (7.4%)	14 (6.7%)	5 (3.2%)	17 (12.0%)	0	5 (7.5%)
Abdominal tenderness	0	1 (11.1%)	0	2 (1.0%)	0	1 (0.7%)	4 (7.3%)	0
Constipation	0	1 (11.1%)	5 (2.5%)	5 (2.4%)	5 (3.2%)	4 (2.8%)	1 (1.8%)	2 (3.0%)
Duodenitis	0	1 (11.1%)	1 (0.5%)	23 (11.1%)	4 (2.5%)	4 (2.8%)	1 (1.8%)	3 (4.5%)
Erosive duodenitis	0	2 (22.2%)	3 (1.5%)	24 (11.5%)	3 (3.8%)	19 (13.4%)	0	5 (7.5%)
Erosive esophagitis	0	1 (11.1%)	1 (0.5%)	13 (6.3%)	1 (0.6%)	8 (5.6%)	0	2 (3.0%)
GERD	0	1 (11.1%)	2 (1.0%)	8 (3.8%)	1 (0.6%)	5 (3.5%)	1 (1.8%)	1 (1.5%)
Esophagitis	0	1 (11.1%)	3 (1.5%)	1 (0.5%)	5 (3.2%)	13 (9.2%)	0	4 (6.0%)
Vomiting	0	2 (22.2%)	1 (0.5%)	3 (1.4%)	3 (1.9%)	0	0	1 (1.5%)

System Organ Class/ Preferred Term	Age < 50 years		50 – 59 years		60 – 69 years		> 70 years	
	Vimovo N = 14	Naproxen n = 9	Vimovo n = 202	Naproxen n = 208	Vimovo n = 157	Naproxen n = 142	Vimovo n = 55	Naproxen n = 67
Study Participant with ANY Adverse Event	12 (85.7%)	8 (88.9%)	163 (80.7%)	186 (89.4%)	119 (75.8%)	124 (87.3%)	41 (74.5%)	55 (82.1%)
Musculoskeletal & Connective tissue disorder overall	3 (21.4%)	0	15 (7.4%)	20 (9.6%)	12 (7.6%)	8 (5.6%)	8 (14.5%)	11 (16.4%)
Arthralgia	1 (7.1%)	0	1 (0.5%)	6 (2.9%)	3 (1.9%)	3 (2.1%)	0	1 (1.5%)
Muscle spasms	1 (7.1%)	0	4 (2.0%)	1 (0.5%)	1 (0.6%)	0	2 (3.6%)	1 (1.5%)
Osteoarthritis	1 (7.1%)	0	0	3 (1.4%)	2 (1.3%)	1 (0.7%)	2 (3.6%)	0
Infections and infestations overall	2 (14.3%)	2 (22.2%)	41 (20.3%)	38 (18.3%)	26 (16.6%)	21 (14.8%)	8 (14.5%)	11 (16.4%)
Bronchitis	1 (7.1%)	0	5 (2.5%)	6 (2.9%)	3 (1.9%)	2 (1.4%)	1 (1.8%)	0
Upper respiratory Infection	1 (7.1%)	0	15 (7.4%)	7 (3.4%)	5 (3.2%)	7 (4.9%)	0	2 (3.0%)
Pneumonia	0	0	0	2 (1.0%)	1 (0.6%)	1 (0.7%)	0	1 (1.5%)
Gastroenteritis	0	0	2 (1.0%)	0	1 (0.6%)	0	0	0
Viral gastroenteritis	0	0	1 (1.0%)	3 (1.4%)	1 (0.6%)	0	0	0
Fungal infection	0	0	2 (1.0%)	0	0	0	0	0
General Disorders and administration site conditions overall	1 (7.1%)	1 (11.1%)	5 (2.5%)	7 (3.4%)	6 (3.8%)	1 (0.7%)	2 (3.6%)	2 (3.0%)
Peripheral edema	1 (7.1%)	0	0	3 (1.4%)	4 (2.5%)	0	0	1 (1.5%)
Nodule	0	1 (11.1%)	0	0	1 (0.6%)	0	0	0
Noncardiac chest pain	0	0	1 (0.5%)	1 (0.5%)	1 (0.6%)	0	1 (1.8%)	0
Chest discomfort	0	0	0	1 (0.5%)	0	0	0	0

System Organ Class/ Preferred Term	Age < 50 years		50 – 59 years		60 – 69 years		> 70 years	
	Vimovo N = 14	Naproxen n = 9	Vimovo n = 202	Naproxen n = 208	Vimovo n = 157	Naproxen n = 142	Vimovo n = 55	Naproxen n = 67
Study Participant with ANY Adverse Event	12 (85.7%)	8 (88.9%)	163 (80.7%)	186 (89.4%)	119 (75.8%)	124 (87.3%)	41 (74.5%)	55 (82.1%)
Investigations overall	1 (7.1%)	1 (11.1%)	6 (3.0%)	5 (2.4%)	5 (3.2%)	4 (2.8%)	1 (1.8%)	1 (1.5%)
Increased blood creatinine	0	1 (11.1%)	0	0	1 (0.6%)	1 (0.7%)	0	0
Increased blood urea	0	1 (11.1%)	0	0	0	1 (0.7%)	0	1 (1.5%)
Abnormal liver function	0	0	6 (2.9%)	3 (1.4%)	0	0	0	0
Increased blood pressure	0	0	1 (0.5%)	0	0	0	1 (1.8%)	0
Psychiatric disorders overall	1 (7.1%)	0	2 (2.5%)	1 (0.5%)	0	2 (1.4%)	0	1 (1.5%)
Anxiety	1 (7.1%)	0	1 (0.5%)	0	0	0	0	0
Renal and urinary disorders overall	1 (7.1%)	1 (11.1%)	4 (2.0%)	3 (1.4%)	0	1 (0.7%)	0	1 (1.5%)
Nephrolithiasis	1 (7.1%)	1 (11.1%)	2 (1.0%)	0	0	1 (0.7%)	0	0
Nervous System Disorders overall	0	0	15 (7.4%)	9 (4.3%)	13 (8.3%)	13 (9.2%)	9 (16.4%)	3 (4.5%)
Headache	0	0	2 (2.0%)	3 (1.4%)	4 (2.5%)	2 (1.4%)	3 (5.5%)	1 (1.5%)
Dizziness	0	0	2 (1.0%)	2 (1.0%)	0	1 (0.7%)	2 (3.6%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders overall	1 (7.1%)	0	14 (6.9%)	14 (6.7%)	7 (4.5%)	5 (3.5%)	4 (7.3%)	4 (6.0%)
Cough	1 (7.1%)	0	4 (2.0%)	6 (2.9%)	3 (1.9%)	3 (2.1%)	2 (3.6%)	2 (3.0%)

System Organ Class/ Preferred Term	Age < 50 years		50 – 59 years		60 – 69 years		> 70 years	
	Vimovo N = 14	Naproxen n = 9	Vimovo n = 202	Naproxen n = 208	Vimovo n = 157	Naproxen n = 142	Vimovo n = 55	Naproxen n = 67
Study Participant with ANY Adverse Event	12 (85.7%)	8 (88.9%)	163 (80.7%)	186 (89.4%)	119 (75.8%)	124 (87.3%)	41 (74.5%)	55 (82.1%)
Injury, poisoning, and procedural complications overall	0	0	8 (4.0%)	9 (4.3%)	8 (5.1%)	5 (3.5%)	4 (7.2%)	2 (3.0%)
Fracture	0	0	1 (0.5%)	0	2 (1.3%)	1 (0.7%)	1 (1.8%)	1 (1.5%)
Skin and Subcutaneous tissue disorders overall	0	0	7 (3.5%)	7 (3.4%)	4 (2.5%)	6 (4.2%)	2 (3.6%)	2 (3.0%)
Rash	0	0	7 (3.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	1 (1.8%)	0
Cardiac disorders overall	0	0	3 (1.5%)	3 (1.4%)	4 (2.5%)	1 (0.7%)	0	2 (3.0%)
Cardiomegaly	0	0	1 (0.5%)	0	2 (1.3%)	0	0	0
Palpitations	0	0	1 (0.5%)	1 (0.5%)	1 (0.6%)	0	0	1 (1.5%)
Ventricular extrasystoles	0	0	1 (0.5%)	0	1 (0.6%)	0	0	0
Cardiac failure	0	0	0	1 (0.5%)	0	0	0	1 (1.5%)
Coronary artery disease	0	0	0	1 (0.5%)	1 (0.6%)	0	0	0
Pericarditis	0	0	0	1 (0.5%)	0	0	0	0
Myocardial infarction	0	0	0	0	1 (0.6%)	0	0	0
Metabolism and nutrition disorders overall	0	0	3 (1.5%)	2 (1.0%)	0	0	2 (3.6%)	3 (4.5%)
Fluid retention	0	0	1 (0.5%)	0	0	0	0	0

System Organ Class/ Preferred Term	Age < 50 years		50 – 59 years		60 – 69 years		> 70 years	
	Vimovo N = 14	Naproxen n = 9	Vimovo n = 202	Naproxen n = 208	Vimovo n = 157	Naproxen n = 142	Vimovo n = 55	Naproxen n = 67
Study Participant with ANY Adverse Event	12 (85.7%)	8 (88.9%)	163 (80.7%)	186 (89.4%)	119 (75.8%)	124 (87.3%)	41 (74.5%)	55 (82.1%)
Blood and lymphatic disorders overall	0	0	1 (0.5%)	3 (1.4%)	3 (1.9%)	0	2 (3.6%)	2 (3.0%)
Anemia	0	0	1 (0.5%)	2 (1.0%)	3 (1.9%)	0	2 (3.6%)	2 (3.0%)
Lymphadenopathy	0	0	0	1 (0.5%)	0	0	0	0
Hepatobiliary disorders	0	0	1 (0.5%)	1 (0.5%)	0	2 (1.4%)	0	0
Vascular Disorders overall	0	0	1 (0.5%)	4 (1.9%)	5 (3.2%)	2 (1.4%)	0	1 (1.5%)
Hypertension	0	0	1 (0.5%)	4 (1.9%)	4 (2.5%)	2 (1.4%)	0	1 (1.5%)

Reviewer's Table Adapted from Sponsor's Table S2.9 p972 Integrated Summary of Safety

The sponsor also proposed to include adverse events from the supportive safety population in support of the labeling for Vimovo tablets. While trials PN400-307 and PN400-309 were reviewed by Dr. Jin Chen, from DAARP, the medical reviewer verified the common adverse events counts from these supportive trials using the adverse events analysis dataset provided by the applicant in the June 30, 2009, submission. These adverse events may be in the labeling and are summarized in the table below. Overall treatment emergent events occurred in 53.3% of patients taking Vimovo, compared with 49.6% of those taking celecoxib and 51.2% of those taking placebo. Again more treatment emergent adverse events from the SOC of Gastrointestinal disorders were most commonly reported. The smaller incidence of treatment emergent adverse events in the supportive safety population relative to the primary safety population may be attributed to the fact that PN400-307 and PN400-309 were of shorter duration (3 months) than those trials in the primary safety population. One would expect more ulcers and GI related adverse events to occur with longer duration of use.

Table 47 Treatment Emergent Adverse Events Occurring in $\geq 2\%$ of Study Participants in the Supportive Safety Population

Preferred Terms	Vimovo n = 490	Celecoxib n = 488	Placebo n = 246
Dyspepsia	41 (8.4%)	52 (10.7%)	30 (12.2%)
Diarrhea	27 (5.5%)	14 (2.9%)	9 (3.7%)
Upper Abdominal Pain	20 (4.1%)	21 (4.3%)	8 (3.3%)
Constipation	17 (3.5%)	10 (2.0%)	3 (1.2%)
Nausea	17 (3.5%)	15 (3.1%)	9 (3.7%)
Dizziness	15 (3.1%)	4 (0.8%)	5 (2.0%)
Peripheral Edema	15 (3.1%)	6 (1.2%)	3 (1.2%)
Headache	13 (2.7%)	18 (3.7%)	13 (5.3%)
Upper Respiratory Tract Infection	8 (1.6%)	6 (1.2%)	5 (2.0%)
Arthralgia	7 (1.4%)	14 (2.9%)	4 (1.6%)
Cough	7 (1.4%)	3 (0.6%)	7 (2.8%)
Nasopharyngitis	7 (1.4%)	7 (1.4%)	5 (2.0%)
Back pain	6 (1.2%)	14 (2.9%)	5 (2.0%)
Sinusitis	5 (1.0%)	6 (1.2%)	6 (2.4%)
Gastroenteritis, viral	3 (0.6%)	1 (0.2%)	5 (2.0%)
Pyrexia	1 (0.2%)	2 (0.4%)	5 (2.0%)

Reviewer's Table reproduced from Sponsor's Table 5.3.5.3.2.14 p42/2911 Integrated Summary of Safety

Although the sponsor only proposed to include treatment emergent adverse events for the primary and supportive safety populations in the labeling, it is worth briefly looking at the data from the long-term safety population and the expanded safety population. Please note the definitions of both populations again. The long-term safety population included all individuals who entered trial PN400-304. The expanded safety population

included individuals from Phase III trials PN400-301, PN400-302, PN400-304, PN400-307 and PN400-309 and examines only those patients who were assigned to the Vimovo treatment group.

Overall the incidence of treatment emergent adverse events was 73.2% in the long term safety population. This is somewhat consistent with the incidence of treatment emergent adverse events reported in the primary safety population (78.3%) and higher than that seen in the supportive safety population (53.3%). The most commonly reported adverse events were from the SOC of Gastrointestinal disorders (35.6%) and included the preferred terms dyspepsia (7.9%), constipation (5.9%), nausea (5.0%), diarrhea (4.6%), and abdominal pain (11.2%). Again there was some splitting of preferred terms that could represent abdominal pain.

The table below compares the treatment emergent adverse events occurring in $\geq 2\%$ of Study Participants across the Expanded Safety Population, the Primary Safety Population, the Secondary Safety Population and the Longterm Safety Populations. Patients in the Longterm Safety Population had higher rates of abdominal pain, peripheral edema, constipation, sinusitis, arthralgia, influenza and hypertension relative to the Primary Safety Population and the Secondary Safety Population. There was some splitting of terms. In example of this, the medical reviewer combined the terms peripheral edema and edema into one term and found that 5% of patients reported edema in the long term safety population, whereas 1.2% reported edema in the primary safety population and 1.4% developed edema in the supportive safety population. The medical reviewer also looked at specific treatment emergent events that were reported as occurring in less than 2% of the population but were considered relevant because of the known toxicity profiles of the reference listed drugs. There were no differences in the incidence of myocardial infarction across the pooled populations. Only 1 patient experienced a myocardial infarction in Primary Safety and Expanded Safety Populations. There were no occurrences in the other populations. Also the rates of angina, abnormal liver function tests, renal failure, anemia, and pneumonia were similar across the pooled populations. The degree of splitting for the terms that represent elevated liver transaminases was somewhat disturbing. However, when the medical officer combined the terms "increase hepatic enzymes", "transaminase increased", "aspartate transaminase increase", "alanine transaminase increased" and "abnormal liver function tests", there was no substantial difference detected between the trials populations. Elevated liver transaminases were found in 1.3% of the Expanded Safety Population, 1.4% in the Primary Safety Population, 1.2% in the Secondary Safety Population, and 1.3% in the Longterm Safety Population. Patients in the Longterm Safety Population had a slightly higher incidence of elevated blood urea (1.7%) relative to the Primary Safety Population (0.2%) and the Secondary Safety Population (0.8%).

Higher incidences of gastrointestinal adverse events in the Primary Safety Population may be attributed to the fact that some of these outcomes were directly solicited and assessed as primary and secondary tolerability variables per study protocol.

Table 48 Treatment Emergent Adverse Events, Including Gastric and Duodenal Ulcers, occurring in $\geq 2\%$ of Study Participants in the ESP, PSP, SSP and the LSP

Preferred Terms	Vimovo ESP N = 1157	Vimovo PSP N = 428	Vimovo SSP N = 490	Vimovo LSP N = 239
Erosive Gastritis	83 (7.2%)	83 (19.4%)	0	0
Dyspepsia	137 (11.8%)	77 (18.0%)	41 (8.4%)	19 (7.9%)
Gastritis	75 (6.5%)	73 (17.1%)	1 (0.2%)	1 (0.4%)
Diarrhea	64 (5.5%)	26 (6.1%)	27 (5.5%)	11 (4.6%)
Abdominal pain upper	51 (4.4%)	24 (5.6%)	20 (4.1%)	7 (2.9%)
Gastric ulcer	24 (2.1%)	24 (5.6%)	0	0
Nausea	51 (4.4%)	22 (5.1%)	17 (3.5%)	12 (5.0%)
Upper respiratory tract infection	43 (3.7%)	21 (4.9%)	8 (1.6%)	14 (5.9%)
Hiatus hernia	19 (1.6%)	18 (4.2%)	0	1 (0.4%)
Abdominal distension	27 (2.3%)	16 (3.7%)	5 (1.0%)	6 (2.5%)
Flatulence	24 (2.1%)	16 (3.7%)	3 (0.6%)	5 (2.1%)
Esophagitis	16 (1.4%)	15 (3.5%)	0	1 (0.4%)
Constipation	42 (3.6%)	11 (2.6%)	17 (3.5%)	14 (5.9%)
Edema peripheral	32 (2.8%)	4 (0.9%)	15 (3.1%)	11 (4.6%)
Headache	30 (2.6%)	11 (2.6%)	13 (2.7%)	6 (2.5%)
Abdominal pain	18 (1.6%)	10 (2.3%)	7 (1.4%)	1 (0.4%)
Bronchitis	21 (1.8%)	10 (2.3%)	2 (0.4%)	9 (3.8%)
Cough	23 (2.0%)	10 (2.3%)	7 (1.4%)	6 (2.5%)
Urinary tract infection	24 (2.1%)	10 (2.3%)	8 (1.6%)	6 (2.5%)
Dizziness	24 (2.1%)	4 (0.9%)	15 (3.1%)	5 (2.1%)
Abdominal pain lower	24 (2.1%)	9 (2.1%)	4 (0.8%)	11 (4.6%)
Dysgeusia	11 (1.0%)	9 (2.1%)	1 (0.2%)	1 (0.4%)
Erosive duodenitis	9 (0.8%)	9 (2.1%)	0	0
Sinusitis	20 (1.7%)	8 (1.9%)	5 (1.0%)	9 (3.8%)

Preferred Terms	Vimovo ESP N = 1157	Vimovo PSP N = 428	Vimovo SSP N = 490	Vimovo LSP N = 239
Arthralgia	23 (2.0%)	5 (1.2%)	7 (1.4%)	11 (4.6%)
Vomiting	17 (1.5%)	4 (0.9%)	8 (1.6%)	5 (2.1%)
Influenza	12 (1.0%)	4 (0.9%)	3 (0.6%)	5 (2.1%)
Hypertension	19 (1.6%)	5 (1.2%)	5 (1.0%)	9 (3.8%)
Abnormal liver function tests	15 (1.3%)	6 (1.4%)	6 (1.2%)	3 (1.3%)
Myocardial infarction	1 (<0.1%)	1 (0.2%)	0	0
Anemia	24 (2.1%)	7 (1.6%)	10 (2.0%)	7 (2.9%)
Increase Blood Urea	6 (0.5%)	1 (0.2%)	1 (0.2%)	4 (1.7%)
Increased creatinine	3 (0.3%)	1 (0.2%)	0	2 (0.8%)
Transient Ischemic attack	2 (0.2%)	0	0	2 (0.8%)
Cerebrovascular Accident	2 (0.2%)	0	2 (0.4%)	0

7.4.2 Laboratory Findings

Anemia, leukopenia, and thrombocytopenia may occur with NSAID use and require hematological monitoring during long-term therapy. There was no specific pattern of changes across time from baseline in the mean values for hemoglobin, red blood cell count, white blood cell count, or platelets across any of the trials in the Primary Safety Population and Secondary Safety Population.

The mean platelet count was 263.4, 258.8, 257.7, and 263.9 at baseline, 3 months, 6 months, and 12 months respectively. At baseline, the mean white blood cell count was 6.84. The mean values for the white blood cell count were 6.65, 6.56, and 6.89 at 3, 6, and 12 months respectively. No substantial number of study participants experienced clinically significant changes in the differential counts of lymphocytes, monocytes, neutrophils, or eosinophils in the Expanded Safety Population when expanded normal ranges were used.

Summary data is presented for the Expanded Safety Population (ESP) which included the Primary Safety Population, the Secondary Safety Population and the Long-term Safety trial (PN400-304). Ten percent (10%) of patients in the ESP had changes in hemoglobin from high or normal to low. Twenty three (23%) shifted hematocrit from high or normal to low. Per the sponsor, when extended ranges for normal were applied only 2% of the ESP shifted hemoglobin from high or normal to low. However, no justification was given for the extended normal range that was used. At baseline the mean hemoglobin for study participants of the Expanded Safety Population taking Vimovo was 13.76. The mean hemoglobin was 13.37, 13.41, and 13.33 at 3, 6, and 12 months respectively. Hemoglobin decreased by 0.4 ± 0.6 g/dl by Month 3, 0.4 ± 0.7 g/dl by Month 6 and 0.4 ± 0.8 g/dl by Month 12. In the Expanded Safety Population, mean hematocrit decreased by $1.2 \pm 2.1\%$ by Month 3, $0.8 \pm 2.5\%$ by Month 6 and $1.0 \pm 2.3\%$ by Month 23. The Maximum change from baseline hematocrit was 11.4% at Month 6.

The following table illustrates the changes in hemoglobin between all studies and all drugs used in the Phase III trials. In summary when normal ranges were used, patients in the Vimovo arm experienced more shifts from high or normal to low than placebo and celecoxib. However, the shift was similar to that seen with Naproxen.

Table 49 Comparisons in Hemoglobin Changes between all Phase III Trial Populations and Agents

Hemoglobin Parameter	Vimovo					Naproxen		Celecoxib	Placebo
	Primary Safety Population N = 428	Secondary Safety Population N = 490	Longterm Safety Population N = 239	12 Month Completers Longterm Safety N = 135	Six Month Population N = 491	Primary Safety Population N = 426	Six Month Population N = 220	Supportive Safety Population N = 488	Supportive Safety Population N = 246
Mean Decreases (g/dl)	0.5 ± 0.8	0.4 ± 0.7	0.4 ± 0.8	0.3 ± 0.9	0.5 ± 0.8	0.4 ± 0.9	0.4 ± 0.8	0.1 ± 0.7	0.0 ± 0.7
Shifts (High/Normal to Low %)	8.5	10.7	11.3	10.4	8.4	10.9	10.5	6.2	4.5
Extended Shifts (High/Normal to Low %)	1.9	2.7	0.8	0.7	1.8	2.4	2.3	1.7	0
Maximum Decrease (g/dl)	3.8	3.4	3.0	3.0	3.0	5.0	3.6	4.1	2.0
Clinically significant changes by number of patients (percent)	3 (0.7%)	16 (3.3%)	3 (1.3%)	2 (1.5%)	6 (1.2%)	5 (1.2%)	2 (0.9%)	12 (2.5%)	1 (0.4%)

There were no significant group mean or maximum changes in chemistry values for the Expanded Safety Population. As stated previously there were some elevations in ALT and AST (See Section 7.35 above). The medical reviewer noted that most of these changes occurred within the first 2 months of study drug initiation. However, overall group mean and median changes for AST and ALT were similar between treatment arms in the Expanded Safety Population. For the Expanded Safety Population, group mean changes in ALT and AST by 3 months were 0.0 ± 10.3 U/L and 0.5 ± 7.5 U/L respectively. By 6 months group mean changes in ALT and AST were -1.1 ± 12.6 U/L and 0.1 ± 7.8 respectively. By 12 months group mean changes in ALT and AST were -0.3 ± 12.7 U/L and 1.8 ± 11.3 U/L respectively. Group mean changes in bilirubin were -0.03 ± 0.17 mg/dl by 3 months, 0.0 ± 0.2 mg/dl by 6 months, and 0.02 ± 0.16 mg/dl by 12 months. The maximum bilirubin noted at any time point was 3.2 mg/dl in the Expanded Safety Population (ESP).

Seventeen patients (1.5%) of patients in the ESP population showed elevations in creatinine at least 0.5 mg/dl. Two patients (302-531-2576 and 304-502-4062) had elevated creatinine more than 1.0mg/dl. Both of these patients were able to complete their respective trials. Although creatinine levels for these two patients never returned to baseline, they did lower with continued treatment which is somewhat reassuring. Creatinine levels shifted from low or normal to high in 8.8% of ESP study participants. BUN shifted from low or normal to high in 22.6% using normal ranges. When expanded ranges were applied the shifts were 2.9% for creatinine and 0.7% for BUN. Group changes in creatinine were not seen. Mean increases in creatinine were 0.0 ± 0.1 mg/dl, 0.0 ± 0.1 mg/dl, and 0.1 ± 0.1 mg/dl at 3, 6, and 12 months respectively. However, changes in BUN were more common. BUN increased by 2.1 ± 4.4 mg/dl, 2.0 ± 4.6 mg/dl and 1.6 ± 4.8 mg/dl at 3, 6, and 12 months respectively.

An analysis of creatinine increases ≥ 0.5 mg/dl are provided in the table below. The results are interesting. After adjusting for duration of exposure, patients taking Vimovo experience an increase in creatinine more often than those taking Naproxen (one of the primary components of Vimovo) but at the same rate as placebo.

Table 50 Analysis of increases in serum creatinine ≥ 0.5 mg/dl for all Trial Agents

		Vimovo N = 1157	EC Naproxen N = 426	Celecoxib N = 488	Placebo N = 246
	Pt-years	456.78	142.24	101.40	51.62
Creatinine ≥ 0.5 mg/dl increase from baseline	Events	17	4	5	2
	Incidence (%)	1.5	0.9	1.0	0.8
	Per 100 Patient Year Rate	3.7	2.8	4.9	3.9

7.4.3 Vital Signs

Vital signs were collected at each study visit. Summaries were provided using mean change from baseline. Blood pressure was also reviewed as increases of more than 10mm Hg and 20mm Hg.

There were no clinically significant changes in heart rate between baseline and any of the subsequent visits in the Expanded Safety Population. Roughly 43% experienced an increase in systolic BP more than 10mm Hg and 20% experienced an increase more than 20mm Hg. Approximately 5% demonstrated elevations in diastolic BP. Group mean systolic BP increased between 1.0 and 1.9 ± 14.5 to 17.2 mm Hg.

7.4.4 Electrocardiograms (ECGs)

For all Phase I trials, the pivotal Phase 3 trials and supportive Phase 3 trials, ECGs were conducted only during the screening process. Information for this section is based on the long term safety trial (PN400-304). Electrocardiograms were routinely conducted in this trial at the 6 and 12 month visit. ECGs were also conducted for early discontinuation. At baseline 45% of patients of the 239 enrolled had normal ECGs. Fifty five (55%) of enrollees had ECGs that were abnormal but not clinically significant. None of the patients had an ECG that was abnormal and clinically significant. Baseline ECG data was missing for 1 patient. At 6 months, ECG data was available for 166 patients. Of these, 53% had a normal ECG. Based on the sponsor's data, approximately 78% of patients experienced no change from baseline at month 6. Approximately 10% shifted from a normal to not clinically significant abnormal ECG and 12% shifted from an abnormal, not clinically significant to a normal ECG. By the end of the study, no patient shifted from a normal to a clinically significant abnormal ECG and 1.4% shifted from an abnormal not clinically significant ECG to an abnormal clinically significant ECG. Approximately 16% shifted from a normal baseline ECG to an abnormal, not clinically significant ECG. Interestingly 11.7% were reported to shift from abnormal not clinically significant to normal.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies performed.

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of Vimovo was included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

It is expected that Vimovo will be chronically used in patients, therefore the reviewer considered the effects of cumulative dosing on the toxicity profile. This was especially important given some of the issues related to the pharmacokinetic profile of the esomeprazole component. (See the clinical pharmacology review for details.) Per the sponsor, no specific pattern or relationship could be determined from this data. Per the sponsor, there was a consistent distribution of overall treatment emergent adverse events by SOC over the exposure quartiles. Using the JMP software, the medical reviewer was able to verify the data presented in Table 14.3.1.12.1 (page 260 of the study report for Trial PN400-304). However the outcomes were interesting as one may have anticipated that (given the therapeutic drug classes of Vimovo) at least the number of TEAEs for the GI SOC would increase with an increase in the number of doses taken. In the analysis done by the sponsor, the first quartile of 34 patients received 670 doses. The second quartile received between 671-697 doses. The third quartile received between 698 – 722 doses and the last quartile took over 722 doses. The intervals alone may be the reason why no cumulative relationship for dose exposure and treatment adverse events could be detected.

Treatment emergent data by exposure quartiles for the Expanded Safety Population were also included in the submission. The sponsor again concluded that there was generally a consistent distribution of overall treatment emergent adverse events by preferred term and SOC. The only exception was in the SOC of Infections and Infestations, where twice the number of TEAEs occurred in the highest dosing quartiles relative to the lower two quartiles. Similarly hypertension occurred more frequently in the higher dose quartile (2.4%) than in the other three quartiles (2.1%, 1.5% and 0.7% respectively in descending order). The medical reviewer does not concur entirely with these conclusions. The Expanded Safety Population contains data from trials of varying design, duration (3 months, 6 months, and 12 months) and consequently varying dose exposures which creates confounding when trying to establish any correlation or association between adverse events and increasing duration use and dose of exposure. Again the dosing intervals chosen by the sponsor seemed odd and made it difficult to compare the groups. Quartile 1 contained 305 patients who took 1 – 159 doses. Quartile 2 contained 275 patients who took 160 – 176 doses. Quartile 3 contained 290 patients who took between 177 and 356 doses. Quartile 4 contained 287 patients who took over 356 doses. Please refer to Table S4.16 page 2068 of the Sponsor's Integrated Safety Summary.

Using the combined ADSL and ADAE datasets submitted by the sponsor for long-term study (PN400-304), the medical reviewer created a new variable for exposure quartile based on the total number of doses taken by study participants. From that analysis, there was no cumulative relationship for dose exposure and treatment emergent

adverse events. The adverse events seen in those patients taking the highest number of doses may be a better reflection of what can be anticipated with long-term chronic use of the drug. The findings were consistent with what is already known about the reference listed drugs.

The following is the medical reviewer's data. Preferred terms were selected based upon relevance to the therapeutic drug class or if there was a particular concern. This table reports the number of events that occurred in each of the dosing groups. Therefore one patient may have reported more than 1 adverse event.

Table 51 Treatment Emergent Adverse Events by Treatment Exposure PN400-304

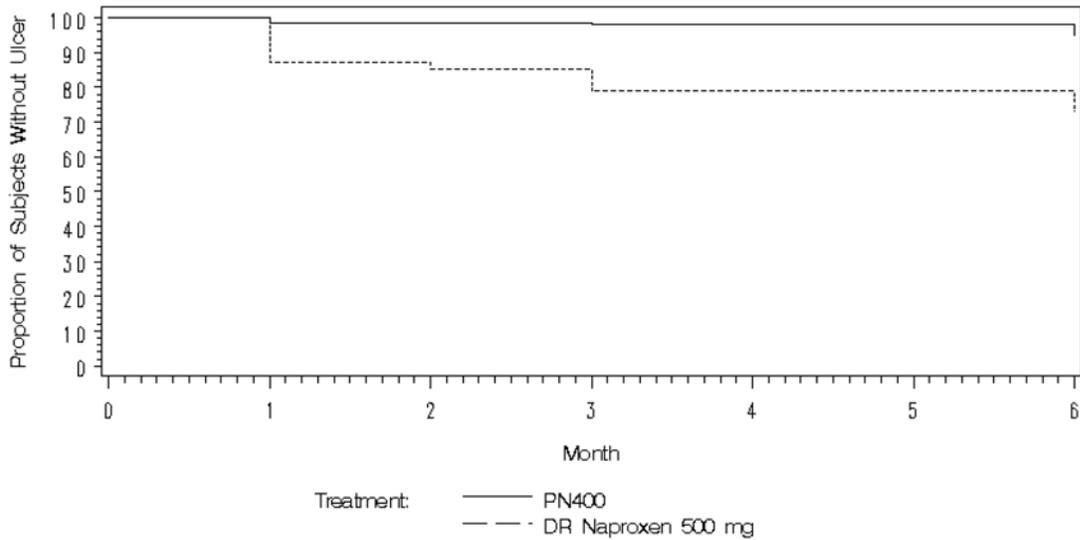
	Overall Safety Population (n = 239) Number of Patients Experiencing an AE (n = 176)			
	0 – 208 Doses N = 29 patients	209 – 417 Doses N = 22 patients	418 – 625 Doses N = 26 patients	>625 Doses N = 99 patients
Gastrointestinal Disorders				
Dyspepsia	9 (31%)	0	2 (7.6%)	10 (10%)
Nausea	2 (6.9%)	2 (9.0%)	1 (3.8%)	11 (11%)
Constipation	4 (13.8%)	4 (18.2%)	3 (11.5%)	4 (4.0%)
Diarrhea	2 (6.9%)	2 (9.0%)	0	11 (11%)
Abdominal pain	0	0	0	1 (1.0%)
Abdominal tenderness	0	0	0	1 (1.0%)
Abdominal pain lower	1 (3.4%)	3 (13.6%)	2 (7.6%)	7 (7.0%)
Abdominal pain upper	1 (3.4%)	2 (9.0%)	2 (7.6%)	3 (3.0%)
Vomiting	1 (3.4%)	0	1 (3.8%)	4 (4.0%)
General disorders and administration site conditions				
Local swelling	0	0	0	1 (1.0%)
Peripheral edema	3 (10.3%)	2 (9.0%)	2 (7.6%)	7 (7.0%)
Localized edema	0	1 (4.5%)	0	1 (1.0%)
Infections and Infestations				
Upper respiratory tract infections	1 (3.4%)	0	1 (3.8%)	14 (14.1%)
Bronchitis	1 (3.4%)	0	3 (11.5%)	7 (7.0%)
Pneumonia	1 (3.4%)	1 (4.5%)	1 (3.8%)	1 (1.0%)
Gastroenteritis	0	0	0	3 (3.0%)
Viral gastroenteritis	0	0	2 (7.6%)	2 (2.0%)
Injury, poisoning and procedural complications				
Fractures	0	0	2 (7.6%)	3 (3.0%)
Investigations				
Hematocrit decreased	0	0	1 (3.8%)	3 (3.0%)

	Overall Safety Population (n = 239) Number of Patients Experiencing an AE (n = 176)			
	0 – 208 Doses N = 29 patients	209 – 417 Doses N = 22 patients	418 – 625 Doses N = 26 patients	>625 Doses N = 99 patients
Hemoglobin decreased	0	0	1 (3.8%)	1 (1.0%)
Red blood cell count decreased	0	0	1 (3.8%)	0
Blood urea increased	0	0	3 (11.5%)	1 (1.0%)
Blood creatinine increased	0	0	1 (3.8%)	1 (1.0%)
Blood pressure increased	0	0	0	1 (1.0%)
Alanine aminotransferase increased	1 (3.4%)	0	0	0
Aspartate aminotransferase increased	1 (3.4%)	0	0	0
Transaminase increased	1 (3.4%)	0	0	0
Vascular disorders				
Hypertension	0	3 (13.6%)	1 (3.8%)	6 (6.1%)
Hypertensive crisis	1 (3.4%)	0	0	0
Renal and urinary disorders				
Acute renal failure	1 (3.4%)	0	0	0
Blood and lymphatic system disorders				
Anemia	0	0	1 (3.8%)	1 (1.0%)
Leukopenia	1 (3.4%)	0	0	0
Cardiac disorders				
Cardiomegaly	1 (3.4%)	0	0	1 (1.0%)
Sinus bradycardia	1 (3.4%)	1 (4.5%)	0	0
Angina pectoris	1 (3.4%)	0	0	0
Atrial fibrillation	0	1 (4.5%)	0	0
Atrioventricular block complete	1 (3.4%)	0	0	0
Atrioventricular block first degree	1 (3.4%)	0	0	0
Bundle branch block	0	0	0	1 (1.0%)
Coronary artery disease	1 (3.4%)	0	0	0
Mitral valve incompetence	0	1 (4.5%)	0	0
Palpitations	1 (3.4%)	0	0	0
Supraventricular extrasystoles	1 (3.4%)	0	0	0
Ventricular extrasystoles	0	0	0	1 (1.0%)
Nervous System disorders				
Transient ischemic attack	1 (3.4%)	1 (4.5%)	0	0

7.5.2 Time Dependency for Adverse Events

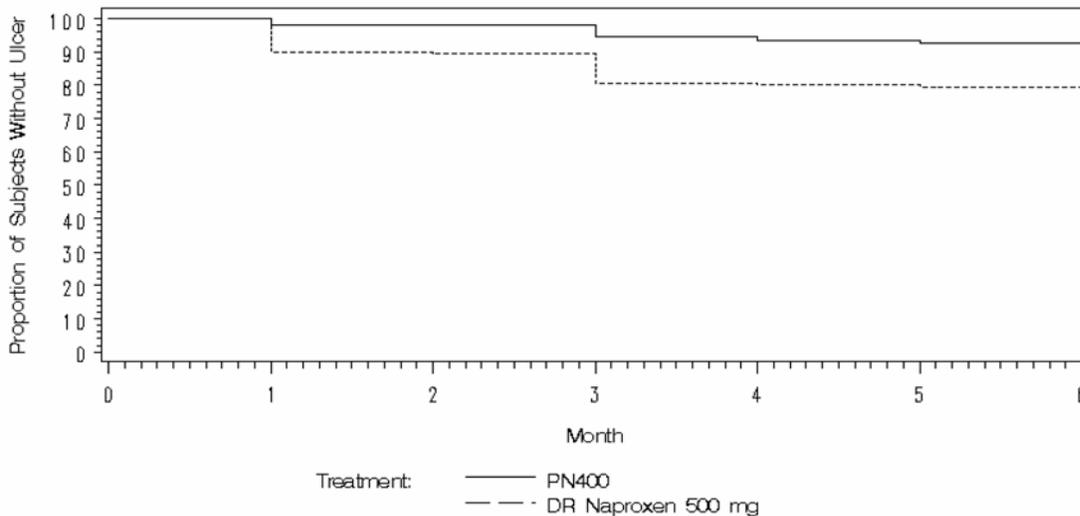
For this submission the primary endpoint may also be considered an adverse event. Therefore survival analysis plots for the time to onset of the primary endpoint (gastric ulcers) for both of the pivotal trials are included below.

Figure 12 Kaplan-Meier Plot of Time to Gastric Ulcer (ITT Population PN400-301)



Sponsor Graph p 172/293 Study Report PN400-301

Figure 13 Kaplan-Meier Plot of Time to Gastric Ulcer (ITT Population PN400-302)



As expected, the proportion of study participants (in both groups) who remained gastric ulcer free decreased with increasing time of drug exposure. However, for both of the pivotal trials, fewer patients in the Vimovo group relative to the Naproxen group developed gastric ulcers over the 6 months trial duration.

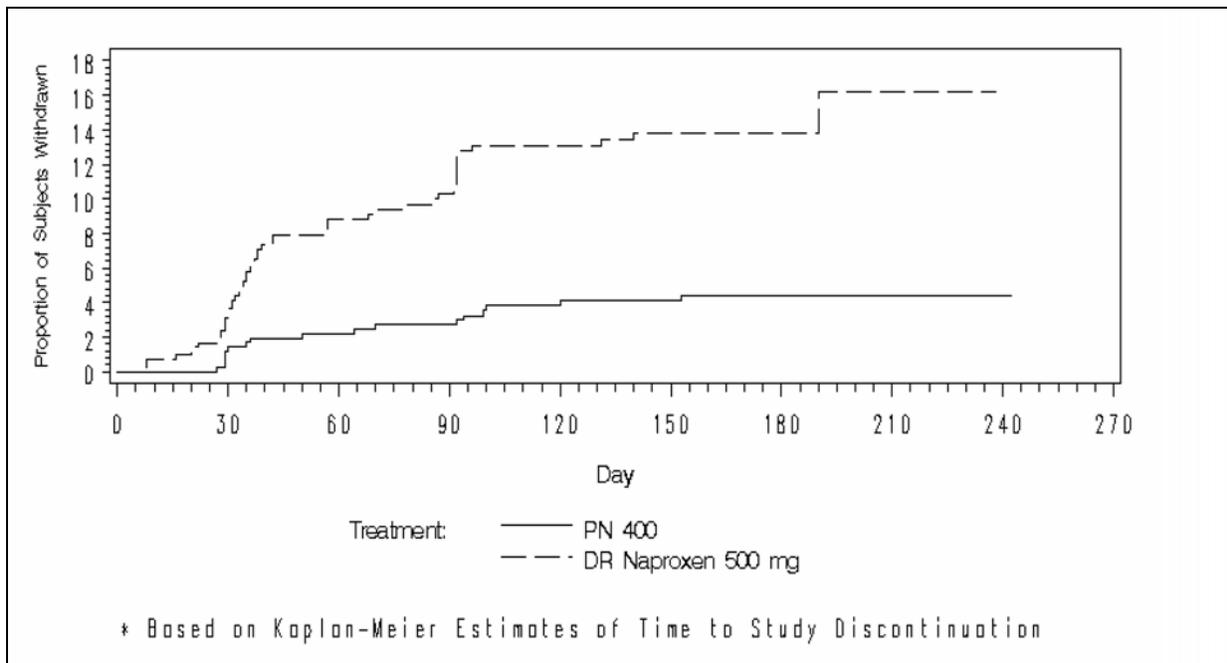
The sponsor also pre-specified NSAID-Associated Upper Gastrointestinal Adverse Events to analyze as secondary endpoints. These events are listed in the table below.

Table 52 Pre-Specified NSAID-Associated Upper Gastrointestinal Events

Upper Gastrointestinal Preferred Terms	
Abdominal discomfort	Erosive Esophagitis
Abdominal pain	Erosive gastritis
Abdominal tenderness	Gastric hemorrhage
Abdominal pain, upper	Gastric mucosal lesion
Duodenal hemorrhage	Gastritis
Duodenal scarring	Gastritis hemorrhagic
Duodenal ulcer hemorrhage	Gastroesophageal reflux disease
Duodenitis	Gastroesophagitis
Duodenitis, hemorrhagic	Gastrointestinal erosion
Dyspepsia	Gastrointestinal hemorrhage
Epigastric discomfort	Gastrointestinal mucosal disorder
Esophagitis	Hyperchlorhydria
Esophageal disorder	Nausea
Esophageal hemorrhage	Reflux esophagitis
Esophageal stenosis	Stomach discomfort
Esophageal ulcer	Varices Esophageal
Erosive duodenitis	Vomiting

The results (from the combined pivotal trials) for Kaplan-Meier estimates of time to study withdrawal due to a prespecified NSAID associated upper GI event are displayed below. As anticipated more patients withdrew due to adverse events in the Naproxen control arms. Most withdrawals occurred in the first 180 days.

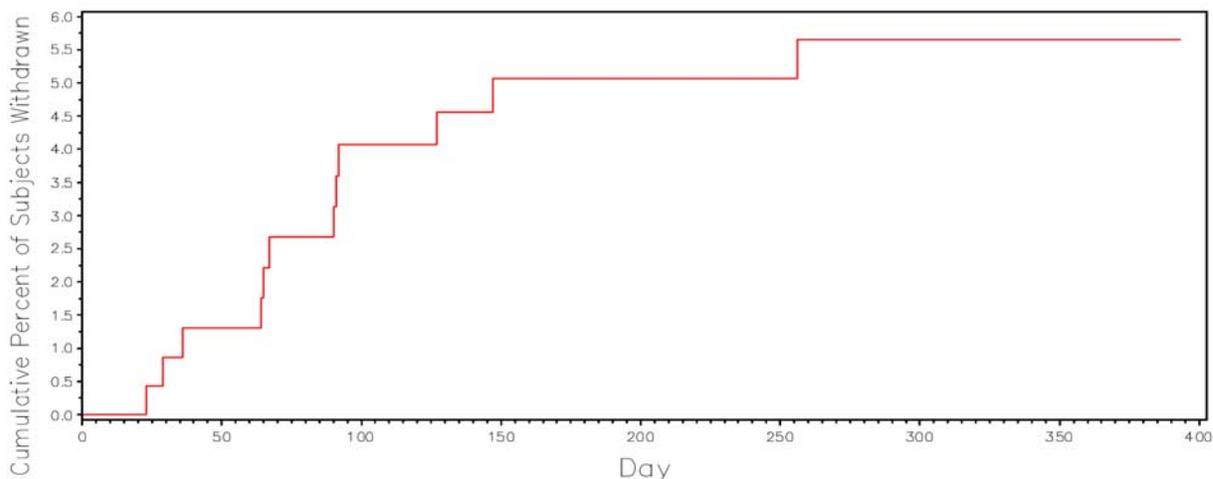
Figure 14 Kaplan Meier Graph Cumulative Incidence of Pre-specified NSAID Associated Adverse Events or Duodenal Ulcers Leading to Trial Discontinuation :ITT Population Trials PN400-301 and PN400-302



Source: Figure E1.26.1 page 57 Sponsor's Integrated Summary of Efficacy page 57/372.

A similar pattern of withdrawals due to adverse events was seen in the long-term study. The Kaplan-Meier Plot for the same pre-specified UGI events are presented in the figure below. Most events occur prior to 150 days.

Figure 15 Kaplan Meier Graph Cumulative Incidence of Pre-Specified NSAID Associated Upper Gastrointestinal Adverse Events Leading to Withdrawal : Overall Safety Population Long Term Trial PN400-304



Source: Sponsor's Figure 14.3.3.5 p.359/440 Study Report Trial PN400-304

In this program there was 1 serious Gastrointestinal Event experienced by a patient taking Vimovo (Patient PN400-304-478-4056) (0.2 events per 100 patient-years). This patient was enrolled in the study on January 3, 2008 and withdrew on February 18, 2008, after taking 116 doses of Vimovo.

Overall, the majority of treatment emergent adverse events (62.6%) in the long-term safety study occurred in the first 180 days. The following table presents the onset of selected treatment emergent adverse events by treatment window in the long-term safety study.

Table 53 Onset of Selected Treatment Emergent Adverse Events by SOC and/or Preferred Term by Treatment Window: 12 month Completers Longterm Safety Trial PN400-304

System Organ Class/ Preferred Term	Days					Overall
	1 – 14	15 - 30	31 – 90	91 - 180	> 180	
All Adverse Events	15 (5.1%)	20 (6.7%)	58 (19.5%)	93 (31.3%)	111 (37.4%)	297
Gastrointestinal Disorders	8 (2.7%)	3 (1.0%)	18 (6.1%)	23 (7.7%)	19 (6.4%)	71 (23.9%)
Dyspepsia	0	1 (0.3%)	1 (0.3%)	3 (1.0%)	1 (0.3%)	6 (2.0%)
Infections and Infestations	3 (1.0%)	4 (1.3%)	14 (4.7%)	11 (3.7%)	27 (9.1%)	59 (19.9%)
Musculoskeletal and Connective Tissue	1 (0.3%)	3 (1.0%)	4 (1.3%)	15 (5.1%)	13 (4.4%)	36 (12.1%)
Arthralgia	0	0	1 (0.3%)	2 (0.7%)	1 (0.3%)	4 (1.3%)
Backpain	0	0	1 (0.3%)	4 (1.3%)	3 (1.0%)	8 (2.7%)
Injury Poisoning and Procedural Complications	2 (0.7%)	1 (0.3%)	7 (2.4%)	14 (4.7%)	3 (1.0%)	27 (9.1%)
Investigations	0	3 (1.0%)	1 (1.0%)	2 (0.7%)	8 (2.7%)	16 (5.4%)
Hematocrit decreased	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	3 (1.0%)
Blood creatinine increased	0	0	0	0	1 (0.3%)	1 (0.3%)
Blood pressure increased	0	0	0	0	1 (0.3%)	1 (0.3%)
Hemoglobin decreased	0	1 (0.3%)	0	0	0	1 (0.3%)
Red blood cell count decrease	0	1 (0.3%)	0	0	0	1 (0.3%)
General Disorders and Administration Site Conditions	0	0	2 (0.7%)	3 (1.0%)	4 (1.3%)	9 (3.0%)
Edema peripheral	0	0	1 (0.3%)	0	1 (0.3%)	2 (0.7%)
Localized edema	0	0	1 (0.3%)	0	0	1 (0.3%)
Edema	0	0	0	1 (0.3%)	0	1 (0.3%)
Vascular Disorders	0	0	0	3 (1.0%)	3 (1.0%)	6 (2.0%)
Hypertension	0	0	0	3 (1.0%)	3 (1.0%)	6 (2.0%)
Cardiac Disorders	0	0	0	1 (0.3%)	2 (0.7%)	3 (1.0%)

Reviewer's Table Adapted from Table 5.3.5.3.2.25 p76 Sponsor's Integrated Summary of Safety

It is important to note that crude incidence rates may underestimate the importance of adverse events in chronically used drugs. Because of the cardiovascular risks associated with NSAIDs, the sponsor gathered a cardiovascular endpoint committee to review and adjudicate all cardiovascular SAEs based on either APT or MACE criteria. (See Appendix 9.5) Results of analysis of the cardiovascular events by study drug are reported by incidence and by patient-year analysis to adjust for the duration of study drug exposure. Per the sponsor, APTC events were low and proportionally similar across treatment groups. MACE events were higher in the Vimovo group relative to the Naproxen due to 3 cases of atrial fibrillation/atrial flutter in the Vimovo group.

Table 54 APTC and MACE Events by Trial Drug all Phase III studies

	Vimovo n = 1166	EC Naproxen n = 426	Celecoxib n = 488	Placebo N = 246
APTC	1 (0.09%) 0.2 events per 100 patient-years	0	0	1 (0.4%) 1.94 events per 100 patient- years
MACE	7 (0.6%) 1.5 events per 100 patient-years	1 (0.2%) 0.8 events per 100 patient-years	1 (0.2%) 0.9 events per 100 patient-years	0

Reviewers Table reproduced from Sponsor's Table p92/2911 Integrated Summary of Safety

Patients in the Vimovo group reported higher rates of edema relative to controls when normalized by patient year exposure. Changes in BUN/Creatinine were similar across all treatment groups. The rate of elevated blood pressure/hypertension in the Vimovo group was higher relative to Naproxen and Placebo. The following table presents the results of the incidence analysis of selected cardiorenal treatment emergent adverse events.

Table 55 Incidence of Analysis of Selected Cardiorenal Treatment Emergent Adverse Events: Expanded Safety Population (All Phase III trials except PN400-303)

		Vimovo N = 1157	EC Naproxen N = 426	Celecoxib N = 488	Placebo N = 246
	Patient Years	456.78	142.24	101.40	51.62
Hypertension/ Elevated BP¹	Events (%)	30 (2.6%)	7 (1.6%)	8 (1.6%)	2 (0.8%)
	Events per 100 patient-year rate	6.6	4.9	7.9	3.9
Edema²	Events (%)	37 (3.2%)	5 (1.2%)	6 (1.2%)	3 (1.2%)
	Events per 100 patient-year rate	8.1	3.5	5.9	5.8
Creatinine/BUN³	Events (%)	8 (0.7%)	3 (0.7%)	4 (0.8%)	1 (0.4%)
	Events per 100 patient-year rate	1.8	2.1	3.9	1.9

Sponsor's Table reproduced from Sponsor's Table 5.3.5.3.2.35 p. 96/2911 Integrated Summary of Safety

1 includes the preferred terms: Blood pressure increased, Hypertension, Blood pressure diastolic increased, Blood pressure systolic increased, and Hypertensive Crisis

2 includes the preferred terms: Fluid retention and any preferred term with Edema

3. includes the preferred terms: Blood creatinine increased, blood urea increased, renal failure, and renal failure acute.

7.5.3 Drug-Demographic Interactions

For each of the system organ classes, the sponsor analyzed treatment emergent adverse events by gender, race, and ethnicity. Overall there were no substantial differences in the rates of treatment emergent adverse events between any of the treatment groups based on race, ethnicity or gender. Analysis by low dose aspirin use was also performed (See section 7.4.1 above also)

The population studied was predominantly white and female. Females reported more adverse events than males (68.3% vs. 63.3%). There were no significant differences in the incidence and distribution of adverse events between Blacks and Whites. Hypertension was reported in 1.9% of Whites and 0.6% of Blacks. Two percent of Whites and 2.5 of Blacks reported cardiac related adverse events. No analysis could be done for other races because of the small numbers. Hispanics/Latinos reported adverse events 70.1% of the time compared with 66.1% of non-Hispanic/Latinos.

Hispanics reported higher rates of dyspepsia, erosive gastritis, and abdominal distension than non-Hispanics. Hispanics also tended to report more headaches and developed more infections than non-Hispanics.

There were no major differences in overall adverse events reported by low-dose aspirin users. Interestingly the overall proportion of GI related adverse events was lower for non low-dose aspirin users than for aspirin users (43.1% vs. 37.1%). However, low-dose aspirin users did report more dyspepsia. Low-dose aspirin users also reported headaches and cough.

7.5.4 Drug-Disease Interactions

Analysis based on patient history of gastrointestinal disorder and cardiovascular disease was performed.

Approximately 50% of patients in the Expanded Safety Population had a prior history of upper gastrointestinal disorders. These patients reported more adverse events than those that did not have a history of GI disease (70% vs. 63%). The difference was largely driven by more reports of erosive esophagitis and gastritis.

Fifty six (56%) of patients in the Expanded Safety Population had a history of cardiovascular disease. The proportion of adverse events was higher in this population (69.3% vs. 63.2%) relative to the trial population who did not have a history of cardiovascular disease. These patients also reported more hypertension (2.1% vs. 1.0%). The risk ratio of developing a cardiovascular complication was over twice as high if a patient had a prior cardiovascular history. Cardiac related adverse events were reported in 2.8% of patients with a prior CV history and in 1.0% of those patients without a history of cardiovascular disease. There was only 1 report of a myocardial infarction in all of the Phase III trials. However, patients with a cardiovascular history experienced more palpitations (0.8% vs. 0.2%) and cardiomegaly (0.6% vs. 0.2%). Patients with a prior cardiovascular history also reported more GI related adverse events (43.4% vs. 39.6%). This was mostly due to increased reports of abdominal pain. Patients with a cardiovascular history also reported more respiratory, infectious and musculoskeletal complaints. Despite, some splitting of the preferred terms under the Investigations SOC, there were no substantial differences between the two groups for changes in liver transaminases, assessments of renal function, and hematological measures.

7.5.5 Drug-Drug Interactions

There are no known interactions between the principal components of this combination product. Current labeling for Nexium reports drug interactions for antiretrovirals; drugs for which gastric pH can affect bioavailability; drugs metabolized by the cytochrome p-450 pathway; and clarithromycin. Naproxen interacts with aspirin, antacids and

sulcalfate, aspirin, cholestyramine, diuretics, lithium, methotrexate, warfarin, and SSRIs. In theory, there is a potential for interaction between Naproxen and other albumin-bound drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional carcinogenicity data was submitted. Per current labeling of naproxen, there is no evidence of tumorigenicity in preclinical trials. Per current labeling for nexium, the carcinogenic potential was assessed using studies from omeprazole, while there was an increased incidence of treatment related enterochromafin cell hyperplasia in preclinical trials, the data was inconclusive.

7.6.2 Human Reproduction and Pregnancy Data

Currently labeling for Nexium labels the drug Pregnancy Category B. Naproxen is Pregnancy Category C. Naproxen containing products are not recommended in labor and delivery. The effects of Vimovo on labor and delivery in pregnant women is not known. Vimovo has been assigned a Pregnancy Category C based on prior preclinical trials and the medical officer concurs with this assignment.

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Proton-pump inhibitor therapy in healthy volunteers may induce acid-related symptoms after withdrawal. This phenomenon called rebound acid hypersecretion was demonstrated after 8 weeks of treatment with a proton-pump inhibitor. If rebound acid hypersecretion does cause acid-related symptoms, there is a potential for PPI dependency.¹⁵

There is limited experience with Nexium overdosage (excess of 240 mg/day). Symptoms are transient and manifestations vary. Patient may experience confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those in the clinical trials.

The drug abuse potential for both nexium and naproxen is small. Per current labeling, of naproxen, naproxen overdosage is characterized by lethargy dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient

alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation, or vomiting. Gastrointestinal bleeding, hypertension, acute renal failure, respiratory depression and coma may also occur. A few patients have experienced convulsions.

No formal abuse or liability studies were done for Vimovo.

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarketing Experience

Vimovo tablets are not currently approved or marketed in any country and therefore there are no post-marketing data on the use of Vimovo tablets. However, both of the individual components of Vimovo are approved in the United States and other countries. Enteric coated naproxen was first approved in the United States, October 14, 1994, under NDA 020067. Nexium, the S-isomer of omeprazole, was approved in the United States February 20, 2001, under NDA 021153. Per the sponsor, the current prescribing of esomeprazole in conjunction with NSAID therapy is supported by current approved labeling for Nexium. There are also clinical guidelines that address the reduction of NSAID associated upper gastrointestinal events in patients at risk of GI toxicity.^{5,11} Naproxen and esomeprazole have been used together for a number of years to decrease the risk of gastric ulcers and upper gastrointestinal adverse events that can result from the chronic use of naproxen. There are no known interactions between naproxen and esomeprazole.

Nexium is indicated for the healing and maintenance of healing of erosive esophagitis; symptomatic gastro esophageal reflux disease; H. pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with antibacterial therapy); pathological hypersecretory conditions including Zollinger-Ellison syndrome, and the risk reduction of NSAID-associated gastric ulcers.

Naproxen is indicated for relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis, acute gout and primary dysmenorrhea.

NSAIDs have been associated with increased risk of nonfatal and fatal cardiovascular and cerebrovascular outcomes, including myocardial infarction and stroke. The available data suggest that naproxen may have one of the more favorable benefit to risk ratios. There is no significant drug-drug interaction that would warrant concern for any new safety issue not already in the currently approved labels of the individual reference drugs. There has been some published data to address the safety and efficacy of

esomeprazole when prescribed with NSAID. However, specific safety information on esomeprazole and naproxen is not provided in these published trials.

Per the sponsor, there have been 67 medically confirmed case reports of adverse events with esomeprazole specifically with concomitant naproxen. Thirty four (34) of these events were serious. That most commonly reported adverse event was pruritis (3 reports). The other adverse events that were reported more than once were arthritis, confusional state, gait disturbance, hypersensitivity, nausea, peripheral edema, decreased platelet count, and decreased white blood cell count. The most common SAE was hypersensitivity (2 reports), peripheral edema (2 reports), and pruritis (2 reports). Most of the AEs reported are already in the one of the currently approved labels.

9 Appendices

9.1 Literature Review/References

Please see Section 10 below.

9.2 Labeling Recommendations

The medical reviewer proposes the following labeling recommendations for the labeling. Please note these labeling recommendations were made prior to formal negotiations with the sponsor.

Section 4 Contraindications:

VIMOVO is contraindicated in patients with known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any of the excipients.

VIMOVO is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [see *Warnings and Precautions* (5.8, 5.13)]. Hypersensitivity reactions, e.g., angioedema and anaphylactic reaction/shock, have been reported with esomeprazole use.

VIMOVO is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

VIMOVO is contraindicated in patients in the late stages of pregnancy [see *Warnings and Precautions* (5.10) and *Use in Specific Populations* (8.1)].

(b) (4)

Medical Officer Comment:

(b) (4)

Section 5.4

Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of an

NSAID, ~~COX-2 inhibitor~~, or aspirin potentiated the risk of bleeding [see *Drug Interactions* (7.2, 7.8)]. Although these studies focused on upper gastrointestinal bleeding, bleeding at other sites cannot be ruled out.

Medical Officer Comment:

Upon review of the articles proposed by the sponsor in support of this statement, the medical reviewer suggests COX-2 inhibitors be deleted as they were not included in the study.

Section 6.1

The safety of VIMOVO was evaluated in clinical studies involving 2317 patients (aged 27 to 90 years) and ranging from 3-12 months. Patients received either 500 mg/20 mg of VIMOVO twice daily (n=1157), 500 mg of enteric-coated naproxen twice daily (n=426), 200 mg of celecoxib once daily (n=488), or placebo (n=246). The average number of Vimovo doses taken over 12 months was 695.6 ± 43.7 .

Medical Officer Comment:

Per current guidelines, it is recommended to include average number of dose and the duration.

The table below lists all adverse reactions, regardless of causality, occurring in >2% of patients receiving VIMOVO from two clinical studies (Study 1 and Study 2) ^{(b) (4)}



Medical Officer Comment:

Per current guidelines it is recommended to include demographics as well as inclusion/exclusion criteria for the current label.

The study was not powered to determine other UGI adverse events. Secondary outcomes were not statistically significant and should be considered exploratory.

Section 6.2

6.2.2 Esomeprazole

The following adverse reactions have been identified during post-approval use of NEXIUM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:

Blood And Lymphatic: agranulocytosis, pancytopenia;
Eye: blurred vision;
Gastrointestinal: pancreatitis; stomatitis;
Hepatobiliary: hepatic failure, hepatitis with or without jaundice;
Immune System: anaphylactic reaction/shock;
Infections and Infestations: GI candidiasis;
Metabolism and Nutritional Disorders: hypomagnesaemia
Musculoskeletal and Connective Tissue: muscular weakness, myalgia;
Nervous System: hepatic encephalopathy, taste disturbance;
Psychiatric: aggression, agitation, depression, hallucination;
Renal and Urinary: interstitial nephritis;
Reproductive System and Breast: gynecomastia;
Respiratory, Thoracic, and Mediastinal: bronchospasm;
Skin and Subcutaneous Tissue: alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

Medical Officer Comment:

The medical officer suggests that postmarketing and clinical experience be separate. The current combination tablet has never been marketed and therefore there is no postmarketing experience for this particular drug. Notwithstanding, if the sponsor is permitted to include postmarketing experience from the reference listed drugs, the medical officer recommends that the sections for naproxen and esomeprazole be listed separately.

Section 8.7

(b) (4)



Medical Officer Comment:

The current drug is not recommended for patients with renal insufficiency. Notwithstanding the current language may imply a contraindication and the reviewer suggests revision

Section 14

(b) (4)



Medical Officer Comment:

Per current guidelines, demographic data is required for the pivotal trials in this section.

Section 17

2. VIMOVO has been developed with esomeprazole to decrease the incidence- (b) (4)
ulceration from naproxen. NSAIDs, including naproxen, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs

and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up [see *Warnings and Precautions (5.4)*].

Medical Officer Comment:

Secondary efficacy endpoints should not be included in the label and overstates the indication of the drug. This is purely promotional in nature and it is suggested that this be deleted.

Medication Guide

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery
- (b) (4)

Medical Officer Comment:

This may imply that Vimovo is contraindicated for this population. The medical officer suggests deletion.

NSAID medicines that need a prescription

Generic Name	TRADENAME
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol) Voltaren
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel

Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, (b) (4)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

Medical Officer Comment:

(b) (4) is no longer marketed and there are no generics, the medical officer suggests removal.

The medication guide contains standard language for all NSAIDs; the sponsor has added Vimovo specific information. This represents a significant modification to the medication guide. Additionally all of the information contained therein should be available in the patient counseling section. The medical officer suggests deletion of the Vimovo-specific language in the medication guide.

9.3 Advisory Committee Meeting

There was no advisory committee meeting held for this NDA.

9.4 Details Individual Trial Designs

9.4.1 Final Trial Protocols for PN 400-301 and PN400-302

Study Design:

This 6 month trial is a Randomized, Double-Blind, Parallel-Group, Active Controlled, Multi-Center Clinical trial to assess the efficacy, tolerability, and safety of Vimovo (aka PN400) tablets in participants at risk for developing NSAID-associated gastric ulcers.

Study Objectives:

Primary Objective:

- To demonstrate that Vimovo tablets (containing 500mg of Naproxen and 20mg of Esomeprazole) is effective in reducing the risk of gastric ulcers in participants at risk for developing NSAID-associated gastric ulcers.

Secondary Objectives:

- To determine if Vimovo is effective in reducing the risk of duodenal ulcers in participants at risk for developing NSAID-associated gastric ulcers
- To compare upper GI symptoms in participants treated with Vimovo versus those treated with Naproxen as measured by the Severity of Dyspepsia Assessment (SODA) instrument and the Overall Treatment Evaluation-Dyspepsia (OTE-DP) instrument. ((The sponsor seeks to show that the PPI in Vimovo will cause a reduction in dyspeptic symptoms (i.e. abdominal pain and discomfort.)))
- To compare heartburn symptoms in participants treated with Vimovo versus those treated with Naproxen.
- To evaluate the safety and tolerability of Vimovo and Naproxen.

Other objective:

- To assess the effect of concomitant use of low-dose aspirin on the incidence of gastroduodenal ulcers within each treatment group.

Patient Population:

Major Inclusion Criteria	Major Exclusion Criteria
<ul style="list-style-type: none"> • Males or non-pregnant, non-breastfeeding females with a history of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or other medical condition expected to require daily NSAID therapy for at least 6 months who are: <ul style="list-style-type: none"> ○ 18 – 49 years old and have a documented, uncomplicated gastric or duodenal ulcer (defined as a mucosal break of at least 3mm in diameter with depth, without any concurrent bleeding, clot, or perforation) within the past 5 years OR ○ 50 years of age or older (these participants do NOT require a history of a documented, uncomplicated gastric or duodenal ulcer within the past 5 years) • Females are eligible for study participation if they are of non-childbearing potential or of childbearing potential and have a negative pregnancy test at screening and agree to use of the acceptable forms of contraception (i.e. those where the lowest expected failure rate is less than 1%) during the study 	<ul style="list-style-type: none"> • History of hypersensitivity to esomeprazole or another PPI • History of allergic reaction or intolerance to any NSAID (including aspirin and/or a history of NSAID-induced symptoms of asthma, rhinitis, and/or nasal polyps) • Presence of uncontrolled acute or chronic medical illness that would endanger a subject if they were to participate in the study • Participation in any study of an investigational treatment in the 4 weeks before screening • GI disorder or surgery leading to impaired drug absorption • Evidence of uncontrolled or unstable cardio- or cerebrovascular disorder, which in the investigator's opinion would endanger a patient if they participated in the trial • Schizophrenia or bipolar disorder • A recent history (in the past 3 mos.) suggestive of alcohol or drug abuse or dependence, including overuse/abuse of narcotics for management of pain • Serious blood coagulation disorder, including use of systemic anticoagulants • Positive test result for <i>H. pylori</i> at screening • Screening endoscopy showing any gastric or duodenal ulcer at least 3mm in diameter with depth • Screening laboratory ALT or AST value >2times the upper limit of normal • Estimated creatinine clearance <30 ml/min • Any screening laboratory value that is clinically significant in the investigator's opinion and would endanger a patient if they were to participate in the trial • History of malignancy (treated or untreated) within the past 5 years, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin.

Treatment:

Randomized patients will receive a study drug and will be instructed to take 2 tablets a day (one in the morning and one in the afternoon/evening) with water, on an empty stomach 30 to 60 minutes before meals. Participants will receive either a 500mg naproxen delayed release tablet or Vimovo (PN400) tablet that contains 500mg of enteric coated naproxen and 20mg of immediate release esomeprazole (as 22.3mg of esomeprazole magnesium trihydrate salt). The naproxen delayed release tablet was designed to be indistinguishable from the Vimovo (PN 400) tablet with regard to size, shape and color. There are no study drug dose adjustments or interruptions allowed.

Concomitant Medications:

Medications Allowed	Medications Prohibited
<ul style="list-style-type: none">• Acetaminophen for supplemental pain management (supplied by sponsor)• Incidental use of liquid antacid (not to exceed 6 teaspoons of 5 ml/day) (supplied by sponsor)• Low-dose (325 mg/day or less) aspirin (if started at least 4 weeks before screening)• Use of antiplatelets (e.g., clopidogrel) (BUT NOT if used concomitantly with aspirin)• Use of inhaled steroids for asthma• Oral corticosteroid therapy (not to exceed >5 mg/day prednisone equivalent, or >10 mg prednisone equivalent every other day)• Methotrexate (not to exceed 20 mg/week)• Monoclonal antibody for rheumatoid arthritis• Intra-articular injections (BUT NOT of NSAIDs) <p>*Episodic use of narcotics for treatment of acute pain or breakthrough pain is allowed for no more than 5 consecutive days and for no more than 3 episodes during the treatment phase.</p>	<ul style="list-style-type: none">• Use of any selective or non-selective NSAID, other than low-dose aspirin and/or acetaminophen during the <u>treatment phase</u>. During the screening phase, use of any selective or non-selective NSAID, is allowed (but must be stopped 14 days prior to initiation of study drug)• Use of any PPI, Histamine-2 receptor antagonist or sucralfate as of 14 days prior to screening to the end of treatment• Misoprostol containing products such as Arthrotec® as of 7 days prior to screening to the end of treatment• Use of anticoagulants (e.g. Coumadin, warfarin, nutritional supplements having anticoagulant properties) from screening to the end of treatment• Other investigational drug(s) from 4 weeks prior to screening to the end of treatment• Use of ulcerogenic medications such as alendronate and risedronate from screening to the end of treatment• Use of non-NSAID analgesics for any of the indication studied, during the treatment phase as it may impact study drug compliance.

Medication Dispensing and Compliance:

Study drug will be dispensed only to study participants who have provided written informed consent and have met all entry criteria. The principal investigator, or designee, shall record the dispensing of the clinical drug to the subject and subsequent returns or losses of drug supply. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the subject.

Study drug will be discontinued for a given study participant if the investigator determines that continuing the study drug may result in a significant safety risk for that participant. Study drug discontinuation will also be required if a patient: 1) develops a gastric or duodenal ulcer 2) becomes pregnant 3) develops a creatinine clearance of less than 30ml/min or 4) has a confirmed drop of hemoglobin $>2.0\text{g/dL}$.

Acetaminophen and liquid antacid will be supplied to the study sites and are to be dispensed to study participants who have provided written informed consent. Only acetaminophen and liquid antacid that was dispensed and returned during the treatment phase will be recorded.

Randomization and Controls:

After all entrance criteria are fulfilled, participants are randomized to one of two treatment groups to receive either 500mg Vimovo (PN400) tablets or 500mg Naproxen tablets, taken orally, twice a day. A randomization list will be produced by a third party using a validated interactive voice response system that automates the random assignment of treatment arms to randomization numbers.

All participants, investigators, study site staff, persons performing assessments and data analysts will remain blinded to the identity of the treatment from the time of randomization until the database lock. Emergency unblinding will be allowed only if knowledge about the assigned study drug is deemed necessary to treat the patient.

Study Visits and Procedures:

The following schematic (taken from the Sponsor Final Amended Protocol) provides information on the visit schedule and assessments:

Figure 16 Visit and Schedule of Assessments for Trial PN400-301 and PN400-302

Visit	Screening (14 days max)		Baseline/ randomization ^a	Treatment		
	1	2		3	4 ^b	5 ^b
Day	14 days		1	30 ± 6	90 ± 12	180 ± 12
Informed consent	X					
In/exclusion criteria	X	X				
Medical history	X		X			
ECG	X					
Laboratory tests	X		X ^d	X	X	X
<i>H pylori</i> test	X					
Pregnancy test ^e	X			X	X	X
Vital signs	X		X	X	X	X
Physical examination	X					X
SODA ^f			X	X	X	X
OTE-DP ^g						X
Heartburn assessment			X	X	X	X
Endoscopy		X		X	X	X
Randomization			X			
Dispense study drug			X	X	X	
Study drug, antacid and acetaminophen accountability				X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Adverse events ^h	X	X	X	X	X	X

^a If the endoscopy result is available at the second screening visit and the subject fulfills all inclusion/exclusion criteria then that subject will be randomized on the same day as the second screening visit; otherwise randomization will occur when the endoscopy results become available.

^b Monthly telephone contacts between Visits 4 and 5, and 5 and 6.

^c End of study assessments should be performed at time of study discontinuation, or if the study endpoint has been reached, if at all possible.

^d Only if screening exceeds 14 days.

^e For women of child bearing potential.

^h SAEs will be captured from time of informed consent, non-serious AEs from the time of first intake of study drug.

This study has two parts: a 2 day screening period and a double-blind treatment period. After all entrance criteria are fulfilled, participants are randomized to one of the two treatment groups (either PN400 or Naproxen 500mg taken orally twice a day). Participants were to have a heartburn assessment and an assessment of dyspepsia and related GI symptoms using the Severity of Dyspepsia Assessment (SODA) instrument on the day of randomization. After initial screening, baseline assessments, and randomization, participants are to return at 1 and 3 months for safety assessments, endoscopy, and additional study drug. At each visit, participants were to have a heartburn assessment and be asked about dyspepsia and related GI symptoms using the SODA instrument. If a gastric or duodenal ulcer is detected, study drug was to be discontinued; the patient discontinued from the study; and the appropriate medication for treatment of the ulcer initiated. Participants completing 6 months of treatment returned for a final visit and procedures including endoscopy. A heartburn assessment, the SODA instrument, and the Overall Treatment for Dyspepsia (OTE-DP) instrument were also administered at the final visit. Serious adverse events were collected from the time of signed informed consent. Nonserious adverse events were collected after initiation of the trial treatment.

Safety Considerations

A physical examination, vital sign recording, and ECG will be done at designated points throughout the study. At screening and at all treatment visits, data will be collected for the following laboratory assessments: creatinine, ALT, AST, hematocrit, alkaline phosphatase, bilirubin, BUN, and Complete Blood Count. Clinically relevant abnormal laboratory values will be repeated. Only those abnormal laboratory values that induce clinical signs or symptoms; are considered clinically significant; require therapy; or fulfill any SAE criteria are reported on the adverse event case report forms.

Adverse events will commence upon study participant taking study drug and will be summarized for each treatment group by System Organ Class and Preferred Term. Tabulations and listings of values and/or parameters for vital signs, clinical laboratory and physical examinations will be presented.

An Adverse Event (or Adverse Experience) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All Adverse events are recorded along with the following information: 1) severity grade (mild, moderate, severe) 2) relationship to the study drug (related/unrelated) 3) duration and 4) whether the adverse event constitutes a serious adverse event. Medical conditions/diseases present before starting study drug are considered adverse events only if they worsen after starting study drug. Although, heartburn and dyspepsia information is collected separately, any reported AE related to heartburn or dyspeptic symptoms will be recorded on the Adverse Events case report

forms provided that the symptoms were reported spontaneously or derived through non-directive questioning.

Abnormal laboratory values or test results constitute adverse events only if they 1) induce clinical signs and symptoms 2) are considered clinically significant 3) require therapy or 4) fulfill any SAE criteria.

A detected AE will be followed until resolution or as long as medically indicated as deemed by the investigator. Assessments will be made at each visit of any changes in the AE severity; its relationship to study drug; interventions required to treat the AE; and the outcome.

A Serious Adverse Event (SAE) is defined as an event that:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Every SAE, regardless of suspected causality, occurring after the participant signs informed consent until 4 weeks after the participant has stopped study participation must be reported.

Efficacy and Endpoint Measures

The data from the Intent-to-treat (ITT) population will be utilized for the primary analysis of the primary efficacy variable, secondary variables, and tolerability variables.

Primary Efficacy Variable

- The primary efficacy variable is the incidence of gastric ulcers at any time throughout 6 months of treatment. Note: An ulcer is defined as a

mucosal break of at least 3 mm in diameter (measured by close application of open endoscopic biopsy forceps) with depth. Endoscopies will be performed during screening and at 1, 3, and 6 months during the treatment period.

Secondary Efficacy Variable

- The key secondary efficacy variable is the incidence of duodenal ulcers at any time during the 6 months of treatment. Note: The same definition of ulcer as defined in the primary endpoint also applies.
- At months 1, 3, and 6 a PRO outcome will be assessed using the SODA instrument. Baseline score, post-baseline score, and change from baseline will be tabulated separately for each SODA subscale (pain intensity, non-pain symptom, and satisfaction) for each treatment group.
- Heartburn Severity (none, mild, moderate, severe) will be recorded for each participant at each visit. The percentage of participants with heartburn resolution (defined as “none” for the heartburn severity question) will be tabulated by the baseline severity for each treatment group.
- Overall treatment evaluation on dyspepsia (better, the Same or Worse) will be collected at final visit using the OTE-Dyspepsia instrument. The percentage of participants with each of the three possible responses, together with the follow-up response on Better and Worse rating will be tabulated for each treatment group.

Other Efficacy Variable:

The other efficacy variable is the incidence of gastric or duodenal ulcers at anytime throughout the 6 months of treatment by low-dose aspirin use at randomization.

Tolerability Variables:

- A key tolerability variable is the proportion of participants with UGI AEs or with duodenal ulcers.
- Another key tolerability variable is the proportion of participants discontinuing the study due to UGI AEs or due to duodenal ulcers
- The proportion of participants discontinuing the study due to *any* AEs.

Statistical Considerations:

All statistical tests will be two-sided and the statistical significance will be tested at 5% level. The intent-to-treat population will consist of all randomized participants who receive at least one dose of study drug and have no ulcer detected by endoscopy at screening. All efficacy analyses will be performed using the intent-to-treat population. Following the intent-to-treat principle, participants will be analyzed according to the

treatment they are assigned to at randomization. All participants in the intent-to-treat population who do not violate the protocol in any major way that would impact the evaluation of efficacy will constitute the Per-Protocol (PP) population. Participants excluded from the PP population will be identified prior to unblinding of the treatment code and the reason for exclusion will be documented. The safety population will consist of all randomized participants who receive at least one dose of study drug.

The analysis of the primary efficacy variable will use a log-rank test stratified by low-dose aspirin use (YES/NO) at randomization. Comparisons of the key secondary efficacy and tolerability endpoints will be in predefined sequential order. The hierarchical fixed-sequence testing approach will be used to adjust for multiple comparisons. These endpoints will be tested in the specified sequence with the rule that once a p-value exceeds 0.05, endpoints further down in the sequence will not be claimed for statistical significance.

Protocol Amendments:

Stamp Date	Protocol Changes
September 17, 2007	To update the Emergency Contact Information To include the term “non-breastfeeding” in the Inclusion Criteria To modify wording regarding pregnancies occurring during the study to include pregnancies in partners of male subjects To modify the period of time that study participants are not allowed to use a PPI, H2 blocker, or sulcrafate To clarify the definition of a “completed subject” so that a participant is considered to have completed the study if either of the following criteria is met 1) completion of 6 months of study drug treatment and the 6 month endoscopy OR 2) endoscopic confirmation of a gastric ulcer at any time during study drug treatment including at the 6 month visit. (If a duodenal ulcer is detected at anytime during the study drug treatment, including the 6 th month visit, the participant will be withdrawn and will not be considered as completing the study. To clarify the dispensing of acetaminophen and antacid To modify recording of study drug dispensation To provide guidance on issuing numbers to participants who are re-screened.
June 17, 2008	To modify the “other” objectives to include an assessment of the effect of concomitant low-dose aspirin use on the incidence of <u>gastroduodenal ulcers</u> within each treatment group. To modify efficacy variables to include “the incidence in gastroduodenal ulcers at any time throughout 6 months of treatment by low-dose aspirin use at randomization (Yes/No). To update the exclusion criteria to exclude participants who had previously participated in a PN400 (aka Vimovo) study. To update the statistical analysis section, modifying wording regarding acetaminophen and antacid and add clarification on AE and concomitant medication recording. (Note the final statistical analysis plan for Study PN400-301 is identical to the statistical analysis plan for Study PN400-302.)

9.4.2 Final Trial Protocol for Trial PN400-304

Study Design:

This is a 12 month open-label multi-center clinical study to evaluate the safety of PN400 (Vimovo) tablets.

Study Objectives:

The primary objective of this study was to evaluate the long-term safety of PN 400 in subjects at risk for developing NSAID-associated upper gastrointestinal ulcers

Patient Population:

Major Inclusion Criteria	Major Exclusion Criteria
<ul style="list-style-type: none"> • Male or non-pregnant female subjects with a history of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or other medical condition expected to require daily NSAID therapy for at least 12 months who are <ul style="list-style-type: none"> ▪ 18-49 years of age and have a history of a documented uncomplicated gastric or duodenal ulcer (a mucosal break of at least 3 mm in diameter with depth, without any concurrent bleeding, clot, or perforation) with in the past 5 years OR who are ▪ 50 years of age and older (those subjects do not require a history of a documented, uncomplicated gastric or duodenal ulcer within the past 5 years.) 	<ul style="list-style-type: none"> • History of allergic reaction or intolerance to any NSAID (including aspirin) and/or a history of NSAID-induced symptoms of asthma, rhinitis, and/or nasal polyps • Presence of uncontrolled acute or chronic medical illness, e.g. gastrointestinal disorder, hypertension, diabetes, thyroid disorder, depression and/or infection that would endanger a subject if they were to participate in the study • Gastrointestinal disorder or surgery leading to impaired drug absorption • Evidence of uncontrolled, or unstable cardio- or cerebrovascular disorder, which in the investigator’s opinion would endanger a subject if they were to participate in the study • Serious blood coagulation disorder, including use of systemic anticoagulants • Positive test for H. Pylori at screening • Baseline endoscopy showing any gastric or duodenal ulcer at least 3mm in diameter with depth • Screening laboratory values for ALT or AST > 2 times the upper limit of normal • Estimated creatinine clearance <50ml/min • History of malignancy (treated or untreated) within the past 5 years with the exception of successfully treated basal cell or squamous cell carcinomas of the skin,

Treatment:

All trial participants were treated as outpatients. Patients were instructed to take a Vimovo tablet (containing 500mg of Naproxen and 20 mg of Esomeprazole) once in the morning and once in the afternoon/evening. Patients were instructed to take the tablets on an empty stomach 30 to 60 minutes before meals.

Concomitant Medications:

Medications Allowed	Medications Prohibited
<ul style="list-style-type: none"> ▪ Acetaminophen for supplemental pain management (supplied by sponsor) ▪ Incidental use of liquid antacid (supplied by sponsor) ▪ Low-dose (325 mg/day or less) aspirin ▪ Use of antiplatelets (e.g., clopidogrel) (BUT NOT if used concomitantly with aspirin) ▪ Use of inhaled steroids for asthma ▪ Oral corticosteroid therapy (not to exceed >5 mg/day prednisone equivalent, or >10 mg prednisone equivalent every other day) ▪ Methotrexate (not to exceed 20 mg/week) ▪ Monoclonal antibody for rheumatoid arthritis ▪ Intra-articular injections (BUT NOT of NSAIDs) 	<ul style="list-style-type: none"> ▪ Use of any selective or non-selective NSAID, other than low-dose aspirin and/or acetaminophen. During the screening phase, use of any selective or non-selective NSAID is allowed ▪ Use of any PPI or H2 receptor antagonist ▪ Misoprostol containing products such as Arthrotec® ▪ Use of anticoagulants (e.g. Coumadin, nutritional supplements having anticoagulant properties) ▪ Other investigational drug(s) ▪ Use of ulcerogenic medications such as alendronate and risedronate ▪ Use of non-NSAID analgesics for any of the indications studied. During the screening phase, use of non-NSAID analgesics is allowed

Episodic use of narcotics for treatment of acute pain or breakthrough pain is allowed for no more than 5 consecutive days and for no more than 6 episodes during the treatment phase.

Medication Dispensing and Compliance:

At the baseline visit (Visit 3), participants received enough medication to allow for 36 days of dosing. At the subsequent visit (Visit 4), study participants received enough medication for 72 days of dosing. At Visits 5, 6, and 7, study participants received 6 bottles of 36 tablets, enough for 108 days of dosing. Study drug provided at each visit was sufficient to last until the next planned visit. All dosages prescribed and dispensed to the study participants who provided written informed consent and met all entrance criteria were recorded on the Study Drug Administration eCRF.

Compliance was assessed by the investigator and/or study personnel at each visit using pill counts and information provide by the study participants.

Randomization and Controls:

This was an open label study that did not require randomization.

Study Visits and Procedures:

Visit	Screening (14 days max)		Baseline ^a	Treatment Period				
	1	2	3	4 ^b	5 ^b	6 ^b	7 ^b	8 ^c
Day			1	30± 6	90 ± 12	180 ± 12	270 ± 12	360 ± 12
Informed consent	X							
In/exclusion criteria	X	X						
Medical history	X		X					
ECG	X					X		X
Laboratory tests	X		X ^d	X	X	X	X	X
<i>H pylori</i> test	X							
Pregnancy test ^e	X			X	X	X	X	X
Vital signs	X		X	X	X	X	X	X
Physical examination	X							X
Endoscopy		X						
Dispense study drug			X	X	X	X	X	
Dispense antacid and acetaminophen (when necessary)	X	X	X	X	X	X	X	
Study drug, antacid and acetaminophen compliance				X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
Adverse events ^f	X	X	X	X	X	X	X	X

^a If the endoscopy result is available at the second screening visit and the subject fulfills all inclusion/exclusion criteria then that subject will be dispensed study drug on the same days as the second screening visits. ^b Monthly telephone contact between Visits 4 and 5, 5 and 6, 6 and 7, and 7 and 8. ^c End of study assessments must be performed at time of study discontinuation if at all possible. ^d Only if screening exceeds 14 days ^e For women of childbearing potential. ^f SAEs will be captured from the time of informed consent, non-serious AEs from the time of first intake of study drug.

After informed consent is signed and eligibility is confirmed, study participants will receive Vimovo (500mg Naproxen/20mg esomeprazole) which is to be taken orally twice a day. Follow-up visits will occur at 1, 3, 6, 9 and 12 months from the day of the first dose of study drug. At the 1, 3, 6, and 9 month visit, patients will have safety

assessments and receive additional study medication. Between clinic visits site staff will contact study participants monthly by telephone.

Interim endoscopies will only be done if clinically indicated. Those patients who develop an endoscopically confirmed ulcer (either gastric or duodenal) during the 12 months of study treatment will be taken off study drug, discontinued from the study and appropriate treatment will be provided. A study participant is considered to have completed the study if they complete 12 months of therapy and all scheduled assessments.

Safety Considerations

At screening and all treatment visits, data was collected for the following laboratory tests: Creatinine, ALT, AST, hematocrit, alkaline phosphatase, sodium, potassium, calcium, magnesium, albumin, blood glucose, bilirubin, BUN, and CBC.

Study drug was to be discontinued for any study participant if the investigator determined that continuing the drug may result in a significant safety risk for that study participant. Study drug was also discontinued for ulceration detected at endoscopy, pregnancy, creatinine clearance less than 30ml/min or a confirmed decrease in hemoglobin by >2.0g/dl. Study participants who were discontinued from the study because of development of ulceration, received appropriate medication for treatment of the ulcer. Study participants who discontinued study drug or prematurely withdrew from the study were to be scheduled for a final visit and all assessments.

The study protocol used a standard regulatory definition for an adverse event and a serious adverse event. An Adverse Event (or Adverse Experience) was defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.”

The occurrence of an adverse event was sought by non-directive questioning of the study participants at each study visit. Adverse events were also detected when they were volunteered by the study participant during or between visits or through physical examination, laboratory test, or other assessments.

All adverse events occurring from the start of study medication administration through the final follow-up visit were recorded on the Adverse Events eCRF with the following Information: the severity grade (mild, moderate, severe); relationship to the study drug(s) (related/unrelated); duration (start and end dates or if continuing at final exam); and whether it constituted a serious adverse event (SAE).

An SAE is defined as an event that:

- is fatal or life-threatening

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Every SAE, regardless of suspected causality, occurring after the study participant signs informed consent and until 4 weeks after the subject has stopped study participation was reported to the study Medical Monitor within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE was to be reported as follow-up to the original episode, regardless of when the event occurs. All reports were to be submitted within 24 hours after the investigator receives the follow-up information. An SAE that was considered completely unrelated to a previously reported one was reported separately as a new event.

Information about all SAEs was collected and recorded on the Serious Adverse Event Report Form. The investigator assessed the relationship to study drug, completed the SAE Report Form and conveyed all information to the study Medical monitor.

The investigator was responsible for notifying the appropriate IRB of all SAEs, including any significant follow-up information.

Efficacy and Endpoint Measures:

Efficacy endpoints were predefined. Adverse event, serious adverse event, laboratory, physical exam, vital sign and ECG data was collected and used for the primary safety analysis.

Statistical Considerations:

Two hundred study participants were recruited to ensure that at least 100 individuals had 12 months of exposure to the Vimovo tablet twice a day.

The safety population will consist of all enrolled study participants who received at least one dose of the study drug. Data will be summarized by reporting the frequency and percentage of study participants in each category for categorical/nominal and ordinal variables. Means, standard deviations (SD), medians, minimum value and maximum values will be summarized and reported for data from continuous variables.

Demographic, background characteristics, baseline medical history, prior and concomitant medications, and treatment exposures will be summarized using descriptive statistics. Treatment compliance over the entire duration of the study will be defined as the percentage of drug days out of the total study days.

An adverse event will be summarized in the treatment phase if it occurred on or after the date of the first study drug and prior to or on the day of the last visit. If an AE has partial or missing start date, it will be treated as treatment emergent unless the partial date excludes that possibility. All adverse events were coded using MedDRA. The incidence of adverse events tabulated by SOC and preferred term. The incidence of adverse events was tabulated by severity and relationship to study drug. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given subject. For summaries by relationship to study drug, the most related occurrence for a particular preferred term will be used for a given subject.

Serious adverse events will be summarized and listed. In addition, adverse events leading to study participant discontinuation will be summarized separately.

Changes in laboratory assessments will be analyzed as shifts from baseline for each study visit. In addition, the clinical laboratory values at baseline, at each post-baseline visit and change from baseline will be summarized using descriptive statistics. Clinically significant laboratory values will be listed by subject and will include all laboratory values prior to and subsequent to the significant value. Physical examination and ECG data will be summarized by study visit. Vital signs at baseline, each post-baseline visit and change from baseline will be summarized using descriptive statistics.

9.5 APTC Endpoints and non-APTC MACE Endpoints: Cardiovascular SAEs

Antiplatelet Trialists Evaluation (APTC) Events

- I. Non-Fatal Myocardial Infarction: the presence of two of the following criteria
 - a. Chest pain
 - b. Any abnormal value of cardiac enzymes (MB fraction of creatinine phosphokinase and/or troponin)
 - c. Current myocardial injury or development of Q waves in 2 contiguous leads of the electrocardiogram
- II. Non-Fatal Stroke: Ischemic or hemorrhagic stroke defined as an acute, focal neurologic event that persisted for >24 hours. Confirmation by imaging studies (magnetic resonance imaging or computerized tomography of the brain) will be sought in all cases, but will not be required for adjudication of the event. Stroke is also defined when imaging demonstrates an acute infarct associated with neurologic symptoms/signs that last <24 hours
- III. Cardiovascular Deaths: deaths that were sudden or unexplained or those due to witnessed arrhythmia, congestive heart failure, myocardial infarction, stroke or pulmonary embolism.

Non-APTC Major Adverse Cardiovascular Events (MACE)

- I. Unstable Angina documented by a hospitalization or emergency department visit, not meeting the acute myocardial infarction (MI) definition above, and characterized by ischemic discomfort at rest for at least 10 minutes
- II. Coronary revascularization defined as percutaneous transluminal angioplasty or coronary artery bypass graft surgery
- III. Transient Ischemic attacks documented by a hospitalization, emergency department visit or valid outpatient setting (e.g. Outpatient TIA Clinic) not meeting the CVA definition above, and characterized by focal, transient (<24 hours) neurological signs and symptoms
- IV. Venous and Peripheral arterial vascular thrombotic events defined as evidence of deep venous thrombosis of the lower extremities or pelvis, pulmonary embolism, peripheral arterial embolism and/or occlusion (peripheral gangrene or ischemia).
- V. Congestive heart failure defined as hospitalization due to dyspnea, shortness of breath and/or edema accompanied by auscultatory findings of pulmonary vascular congestion requiring parenteral drug therapy. Radiographic and/or echocardiographic documentation is desirable but not required. .
- VI. Ventricular Arrhythmia, no evidence of ischemia (will require presentation of ECG tracings)
- VII. Atrial Arrhythmia, no evidence of ischemia (will require presentation of ECG tracings)
- VIII. Syncope with a cardiovascular etiology.

10 References

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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/

ERICA L WYNN
04/21/2010

RUYI HE
04/23/2010



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

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Response to Request for Consultation

Date: February 3, 2010

To: Division of Gastroenterology Products (DGP)
ODE-II/OND/CDER

From: Jin Chen, MD, PhD
Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Ellen Fields, MD, MPH
Medical Team Leader

Sharon Hertz, MD
Deputy Director

Bob Rappaport, MD
Division Director
Division of Anesthesia, Analgesia and Rheumatology Products

Re: **NDA 22-511**
Drug name: **Vimovo** (naproxen/esomeprazole) Tablets
Related IND: IND 76,301 (PN400)
Sponsor: Pozen (partner with AstraZeneca)
PDUFA date: April 30, 2010

EXECUTIVE SUMMARY

Two osteoarthritis (OA) trials (Studies 307 and 309) of placebo- and active-controlled non-inferiority design, submitted in support of this application, did not provide

substantial evidence to establish that PN400 tablet twice daily (500 mg naproxen and 20 mg esomeprazole or Vimovo) was non-inferior to celecoxib 200 mg daily for the treatment of signs and symptoms of osteoarthritis. However, as a pre-specified secondary objective in both studies, superiority of PN400 to placebo was established for the indication of the treatment of the signs and symptoms of osteoarthritis based on primary ITT/LOCF analysis and three sensitivity analyses (except the BOCF analysis in Study 309). Together, the bioequivalence of the naproxen in PN400 to the reference drug (EC-Naprosyn) and the superiority of PN400 to placebo provide adequate evidence of efficacy for the proposed indication for this 505(b)(2) application.

(b) (4)

BACKGROUND

The Division of Gastroenterology Products (DGP) requested this consult on July 15, 2009 to seek assistance from DAARP on the review and labeling of NDA 22-511 (Vimovo or PN400). Later, the consult request was clarified and updated by Dr. Erica Wynne (a primary medical officer assigned to this NDA in DGP) through emails:

- August 17, 2009 email: DAARP's evaluation on the safety and efficacy of two osteoarthritis trials "Studies PN400-307 and PN400-309" for the proposed indication and claims in the labeling.
- [REDACTED]

(b) (4)

A separate consult request from DGP was sent to the statistical team covering DAARP to review the endpoints and analyses in Studies PN400-307 and PN400-309. The primary statistical reviewer is Ms. Katherine B. Meaker.

This memo will focus on the efficacy and safety reviews of the two OA trials (Study 307 and Study 309) and requirements for pediatric studies to fulfill PREA. The labeling review will be performed separately.

REGULATORY HISTORY

DAARP was previously consulted on the study design of the two OA trials (Studies 307 and 309) for this product under IND 76,301 for the following two meetings:

- Post-EOP2 meeting on June 10, 2008
- Pre-NDA meetings on March 23, 2009

At both meetings, the following guidance was conveyed to the Sponsor during the meeting and later through the meeting minutes:

1. [REDACTED] However we disagree with your proposed analyses of the two studies planned to assess the efficacy of PN 400 in patients with OA of the knee using

(b) (4)

(b) (4)

2. **Analysis population:** The analyses of efficacy endpoints in the proposed trials should be conducted on the intent-to-treat population and the per-protocol population.
3. **Primary endpoint** must be the change from baseline to the end of treatment (12 weeks) in WOMAC Pain, WOMAC Function and Patient Global Assessment.
4. **Handling dropouts:** a conservative imputation method for dropouts should be used as most of the dropouts are nonrandom. It is not acceptable to impute a good pain score for patients who cannot finish the study due to either adverse events or lack of efficacy, which is a bad outcome. This is true for comparisons with placebo and comparisons with active comparators.
5. **Pediatric studies** (b) (4)
You are required to submit a pediatric development plan with the NDA. Naproxen is approved for Juvenile Rheumatoid Arthritis (JRA). While NSAID-associated GI adverse events, including gastric ulcer, are less common in pediatric patients, they do occur. Due to its potential GI protective effect, PN400 may be better tolerated in the JRA population compared to naproxen alone.
6. **The GI-related endpoints** (b) (4)
7. **Substantial evidence** of analgesic efficacy of PN400 will be based on bioequivalence to EC-Naprosyn, and the Studies 307 and 309 are intended to demonstrate comparability of PN-400 to celecoxib.

PROPOSED PRODUCT

The proposed product, PN400 tablets or Vimovo (approved trade-name), is a fixed-dose combination of naproxen (375 mg or 500 mg) and esomeprazole (20 mg). The tablet is formulated as an inner enteric-coated (EC) naproxen with an outer film coat of immediate-release esomeprazole.

PROPOSED INDICATION

The proposed indication is a modified combination of the indications of the two reference drugs, EC-Naprosyn and Nexium:

VIMOVO (b) (4) indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers. (b) (4)

(b) (4)
VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen containing products.

There are two deviations in the proposed indication from the reference drugs:

(b) (4)

PROPOSED DOSING REGIMEN:

One tablet (naproxen/esomeprazole: 375/20 mg or 500/20 mg) bid.

The regimen is within the recommended dose range for EC-Naprosyn (250-500 mg bid) and Nexium (20-40 mg qd for up to 6 months).

CLINICAL DEVELOPMENT PROGRAM

The product was developed under a 505(b)(2) application using the following two reference drugs:

- **EC-Naprosyn** (enteric-coated naproxen) under NDA 20-067 held by Roche. A Patent Certification was submitted with the NDA
- **Nexium** (enteric-coated esomeprazole) under NDA 21-153 held by AstraZeneca (a partner of the Applicant). An Authorization Letter was submitted with the NDA.

The following seven clinical trials were submitted to support this 505(b)(2) NDA, which were considered pivotal as per the Applicant:

- **Three bioequivalence studies (single dose):** Studies 102, 114 and 105 to establish bioequivalence of naproxen in PN400 tablets vs. EC-Naprosyn
- **Two GI safety trials:** Studies 301 and 302 to compare PN400 with EC-Naprosyn in the incidence of endoscopic gastric ulcers
- **Two osteoarthritis trials:** Studies 307 and 309 to establish comparability of PN400 with celecoxib in analgesic effects.

OSTEOARTHRITIS TRIALS

The two OA trials, Study 307 and Study 309, were submitted to assess *comparability of PN400 with celecoxib* for the treatment of signs and symptoms of OA (primary objective) and in *GI tolerability* (one of secondary objectives). The following is the overall review of both studies (see individual study reviews in Appendix 1 for details):

Study Design:

Both trials were designed identically as 12-week, multi-center, randomized, double-blind, placebo-controlled, active-controlled, non-inferiority (NI) studies. A total of 619 (Study 307) and 615 (Study 309) patients with the knee OA were enrolled from 75-82 study sites in the US and were randomized into three groups with a ratio of 2:2:1 (PN400:celecoxib:placebo). The planned enrollment for each study was 570 patients with a study power of 90% based on the proposed NI margin of 10 mm difference (2-sided 95% CI) in three co-primary endpoints between PN400 and celecoxib. The subjects were treated with PN400 tablets (500 mg naproxen/20 mg esomeprazole) bid, celecoxib capsules 200 mg qd or placebo for 12 weeks.

The standard three co-primary endpoints for the OA indication were used: *the mean change from baseline at Week 12 in WOMAC Pain, WOMAC Function and Patient Global Assessment*. The secondary endpoints included common supportive efficacy variables for OA and variables for GI tolerability.

The primary analysis was a non-inferiority (NI) analysis of PN400 compared to celecoxib in the ITT population with LOCF (Last Observation Carried Forward) imputation for dropouts. Non-inferiority would be established if:

- The upper bound of the 2-sided 95% CI was less than or equal to a NI margin of +10 mm for the differences in WOMAC Pain and WOMAC Function between PN400 and celecoxib (a negative difference favors PN400).
- The lower bound of the 2-sided 95% CI was greater than or equal to a NI margin of -10 mm for the differences in PGA-VAS between PN400 and celecoxib (a positive value favors PN400)

There were four sensitivity analyses to test the primary LOCF imputation, including one pre-specified ITT/without LOCF analysis (for non-inferiority only) and three *post-hoc* analyses. The *post hoc* sensitivity analyses using the ITT population with the following three imputation methods were requested by the Division at the pre-NDA meeting. The BOCF and BOCF/LOCF hybrid are common for testing the effects of LOCF. However, DAARP does not accept LOCF as the method for imputing missing scores due to early drop outs for efficacy studies in OA.

- BOCF (Baseline Observation Carried Forward) imputation for all missing data.
- BOCF/LOCF hybrid imputation with BOCF for lack of efficacy and adverse events and LOCF for other reasons.
- MMRM (Mixed-model Repeated-Measures) by using all data from all subjects who had baseline values without any *ad-hoc* data imputation for missing data.

Secondary analyses included PP/LOCF analysis for non-inferiority (PN400 vs. celecoxib) and superiority (active treatments vs. placebo), ITT/LOCF superiority analysis (active treatments vs. placebo) and comparisons of the effect size between PN400 and celecoxib.

Results:

The Applicant’s analyses (primary and secondary) of the primary endpoints for both non-inferiority (PN400 vs. celecoxib) and superiority (PN400 and celecoxib vs. placebo) were consistent with the re-analyses performed by DAARP’s statistical reviewer (Ms. Katherine Meaker). See the statistical review for details.

Non-inferiority of PN400 compared to celecoxib: The upper bound of the 95% CI of the differences in three co-primary endpoints between PN400 and celecoxib were 4-5 mm, within the pre-specified NI margin of 10 mm, based on the primary analysis, secondary analyses and sensitivity analyses in both studies. Also, the effect sizes of PN400 compared to placebo were similar to and slightly larger than those of celecoxib (Table 1).

However, the pre-specified NI margin is inadequate, as determined by both the clinical and statistical review teams, and the effect sizes were too small as compared with similar OA trials on the similar products. The non-inferiority of PN400 compared to celecoxib cannot be established as demonstrated by the re-analyses of non-inferiority performed by the statistical review team using a re-defined NI margin (see the Discussion for details).

Superiority of PN400 and celecoxib compared to placebo: In both studies PN400 was statistically superior to placebo in all three co-primary endpoints in the primary analysis (Table 1) and sensitivity analyses (except BOCF in Study 309).

Celecoxib was statistically superior to placebo in three co-primary endpoints in Study 307, but failed in Study 309, based on the primary analysis (Table 1) and sensitivity analyses. In addition, with the secondary analysis of the three co-primary endpoints using the per-protocol population with LOCF imputation, both PN400 and Celecoxib failed to demonstrate superiority over placebo in WOMAC Pain and Function scales.

Table 1. Non-inferiority and Superiority analysis of PN400 in ITT population with LOCF imputation

(See Table 7 in the Study 307 review and Table 6 in the Study 309 review in Appendix for details)

Co-primary Endpoints*	Study 307 LS Mean (95% CI)			Study 309 LS Mean (95% CI)		
	PN400 minus Celecoxib	PN400 minus Placebo	Celecoxib minus Placebo	PN400 minus Celecoxib	PN400 minus Placebo	Celecoxib minus Placebo
WOMAC Pain	-0.22 (-4.76, 4.32)	-6.36 (-11.98, -0.73)	-6.14 (-11.75, -0.52)	-1.30 (-5.94, 3.34)	-5.81 (-11.60, -0.12)	-4.56 (-10.28, 1.16)
WOMAC Function	-0.09 (-4.57, 4.38)	-5.78 (-11.32, -0.23)	-5.68 (-11.23, -0.14)	-2.11 (-6.82, 2.60)	-6.59 (-12.41, -0.76)	-4.47 (-10.28, 1.33)
PGA-VAS	-0.47 (-5.08, 4.14)	6.76 (1.14, 12.37)	7.23 (1.56, 12.89)	3.45 (-1.41, 8.31)	7.64 (1.65, 13.63)	4.18 (-1.80, 10.17)

* Least Square (LS) mean changes from baseline at Week 12 and the 95% CI were calculated with ANCOVA as a continuous covariate. A negative change (minus value) in the WOMAC Pain and Function and a positive change in the PGA-VAS indicate improvement and favor to active treatments (vs. placebo) or to PN400 (vs. celecoxib). The 95% CI across “0” suggests a statistically significant difference.

GI tolerability:

As a secondary objective in both studies, the GI tolerability was assessed with secondary endpoints including mSODA, heartburn-free days, incidence of NSAID-associated GI events and rescue antacid use. Except that PN400 showed numerically less GI benefit than celecoxib based on mSODA in Study 307, PN400 appears similar to or slightly better than celecoxib and placebo in all other GI endpoints. However, the GI outcome measures may have been confounded by the high background of NSAID-associated GI disorders because a majority of subjects in both studies had used NSAIDs prior to the study.

Discussion and Conclusion:

Overall, the Applicant followed our clinical guidance that was provided during the EOP2 and pre-NDA meetings for the conduct and analyses of two pivotal osteoarthritis trials to primarily demonstrate comparability between PN400 and celecoxib for the treatment of signs and symptoms of osteoarthritis. The following are our conclusions based on the data submitted in this NDA:

- PN400 (500 mg naproxen/20 mg esomeprazole bid) is efficacious for the treatment of signs and symptoms of osteoarthritis of the knee based on non-primary superiority analyses comparing PN400 with placebo in both trials.
- If the bioequivalence of PN400 to the reference drug EC-Naprosyn (naproxen PK profile) is adequately established, the Applicant's proposed indication "*for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis*" and dosing regimen would be acceptable. However, the "at risk" patient population defined in the proposed indication is pending for discussion during the labeling review.
- The non-inferiority of PN400 (500/20 mg bid) compared to celecoxib (200 mg qd) cannot be established based on the totality of efficacy outcomes from both trials. Mainly, the Applicant's pre-specified NI margin (10 mm) was inadequate based on the observed effect sizes (of celecoxib or PN400 compared to placebo) in both trials.
 - The upper bound of the 95% CI of the observed effect sizes of celecoxib (vs. placebo) were only 0.28-1.75 mm less than the pre-specified NI margin (10 mm) for WOMAC pain and Function in both studies, suggesting that PN400 might be similar to placebo if a non-inferiority is established based on this NI margin.
 - The Division's statistical review team re-defined the NI margin based on the observed effect size of celecoxib and concluded that PN400 was not non-inferior to celecoxib in both studies.
 - In Study 309, non-inferiority comparisons to celecoxib were not suitable to support the efficacy of Vimovo because celecoxib was not statistically significantly different from placebo.
 - In general, a non-inferiority design for an analgesic clinical trial faces big challenges because of the intrinsic limitations of the analgesic trials, such as

large variations (intra-/inter-group), small treatment size, and inconsistent outcomes across studies (often failed trials). This is supported by the failed superiority of celecoxib to placebo (primary analysis) in Study 309 and PN400 to placebo (secondary PP analysis) in Study 307.

- The assessment of GI tolerability in these studies is inconclusive because of the high baseline NSAID-associated GI disorders (majority of subjects used NSAIDs before the study), lack of an appropriate control arm (such as naproxen alone) and lack of objective GI outcome measures.
- No new safety signals have been identified from either study, as compared to the reference drugs.

PEDIATRIC STUDY PLAN

As seen under the above Regulatory History, DAARP provided the following guidances to the Applicant regarding PREA requirements on this product during Pre-NDA meeting:

 (b) (4)

You are required to submit a pediatric development plan with NDA. Naproxen is approved for Juvenile Rheumatoid Arthritis (JRA). While NSAID-associated GI adverse events, including gastric ulcer, are less common in pediatric patients, they do occur. Due to its potential GI protective effect, PN400 may be better tolerated in the JRA population compared to naproxen alone.

The Applicant's submission:

 (b) (4)

Pediatric status of the reference drugs:

Both reference drugs are indicated for pediatric patients as per the current labeling (July 2008 for Naprosyn and June 2009 for Nexium):

- *Naprosyn suspension* is indicated for the treatment of juvenile rheumatoid arthritis (JRA) in patients of 2 years old and above (titrated based on body weight with maximum of 5 mg/kg bid).
- *Nexium* is indicated for the treatment of GERD in patients of age 1-17 years for short-term treatment (20 or 40 mg for 12-17 years old and 10 mg for 1-11 years old, qd for up to 8 weeks), but not for NSAID-associated gastric ulcer (only for high risk patients: age >60 years or ulcer history).

DAARP's Comments:

(b) (4)
the submitted data suggest that pediatric patients with arthritis such as JRA can be a potential target population for this product (see Appendix-2 for details):

- Approximately 300,000 US children under age 18 (or 1 in 250 children) have been diagnosed with arthritis or other rheumatologic conditions, mostly JRA, according to CDC's study in 2007. Unlike JRA, the juvenile AS is much less common, is also difficultly diagnosed and studied in pediatric population.
- Chronic NSAID therapy is the first line of JRA medication and incidence of the NSAID-associated adverse GI reactions is comparable to adult population, although with low severity.
- Estimated incidence of NSAID-associated ulcer in pediatric population (17 years and below) is about 8% based on literature (provided by the Applicant).

Therefore, PN400 tablets, if approved, will likely be used in the JRA patients, like other naproxen single ingredient products. Since the reference drug for PN400, Naprosyn has been approved for JRA (age >2 years) and Nexium for GERD but not for NSAID-associated ulcer, DAARP recommends that the Applicant should have the following pediatric study plan to fulfill PREA requirements and be conducted as post-marketing commitments:

1. Comparative PK studies in pediatric patients age >2 years with an age-appropriate formulation of PN400 (for bridging JRA indication)
2. Comparative PK studies (and efficacy studies) in pediatric patients age >2 years (for bridging NSAID-associated ulcer indication) (defer to DGP regarding whether efficacy of esomeprazole can be extrapolated for the proposed indication to the pediatric age group)
3. Sufficient safety database for PN400 in pediatric population should be established.

Although Ankylosing Spondylitis (AS) does occur in the pediatric age groups, DAARP recommends that pediatric studies be waived in this condition. Historically, waivers for pediatric studies in AS have been granted for DMARDS (disease modifying anti-rheumatoid drugs) due to lack of feasibility. It can be extremely difficult to diagnose specific subsets of juvenile spondyloarthritis since the disease is usually in its earliest stages in pediatric patients, and does not present definitively until adulthood.

APPENDIX 1: individual study reviews of OA trials

Study PN400-307

Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy of PN400 bid and Celecoxib 200 mg qd in Patients with Osteoarthritis of the Knee

Study location: US (79 sites)

Study report date: April 21, 2009

Study period: April 8 to Dec 3, 2008

OBJECTIVES

Primary objective:

To demonstrate that PN400 is non-inferior to celecoxib 200 mg qd in the treatment of the signs and symptoms of osteoarthritis (OA)

Secondary objectives:

- 1) To assess the efficacy of PN400 and celecoxib in the time to onset of improvement (over one week)
- 2) To compare the efficacy of PN400 and celecoxib to each other and to placebo at Weeks 6 and 12
- 3) To compare UGI symptoms
- 4) To evaluate the overall safety and tolerability of PN400 and celecoxib

STUDY DESIGN

Overall design:

A randomized, double-blind, parallel-group, placebo-controlled, active-controlled (non-inferiority), multi-center, 12-week trial

Study subject:

A total of 570 osteoarthritis (OA) patients with moderate-to-severe pain were planned to be recruited from 79 study sites in US using the following criteria:

Key inclusion criteria

- 1) Male or female subjects ≥ 50 years of age with a 6-month history of OA of the knee
 - a. symptomatic OA of the knee meeting ACR criteria for clinical diagnosis of OA
 - b. an ACR functional class rating of I, II or III
 - c. OA flare at the Baseline/Randomization Visit
- 2) Female subjects: non-pregnant or non-childbearing potential or using reliable contraception (for childbearing potential)

- 3) Subjects were required to have been on a stable dose of NSAIDs, COX-2 inhibitors or other oral analgesic therapy for at least 6 weeks and required to continue treatment for 12 weeks. Current oral analgesic therapy was to have been withdrawn at Screening.

Key exclusion criteria

- 1) Subjects with rheumatoid arthritis or gout/pseudo-gout, fibromyalgia syndrome, acute joint trauma at the index joint within the 3 months prior to screening with active symptoms
- 2) Previous (in the past 12 months) or anticipated need for surgical or invasive procedure performed on the index joint during the study
- 3) Subjects with intra-articular or intramuscular corticosteroids or intra-articular hyaluronic acid injections within 8 weeks prior to randomization
- 4) Presence of uncontrolled acute or chronic medical illness, e.g. morbid obesity, GI disorder, diabetes, active GI disease, chronic or acute renal or hepatic disorder, depression and/or infection, etc, that would endanger a subject if the subject were to participate in the study
- 5) GI disorder (e.g., severe erosive esophagitis, Zollinger Ellison syndrome) or surgery leading to impaired drug absorption, peptic ulcer disease within 6 months prior to Screening
- 6) Screening laboratory value for alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 2 times the upper limit of normal
- 7) Estimated creatinine clearance < 30 ml/min

Treatment:

Subjects were to have been randomized at 2:2:1 to receive one of the following treatments (1 tablet and 1 capsule in AM 30-60 minutes before breakfast and 1 tablet in PM 30-60 minutes before dinner):

- PN400 (n=228): enteric-coated naproxen 500 mg/immediate-release esomeprazole 20 mg tablets, 1 tablet bid (AM and PM)
- Celecoxib (n=228): overencapsulated Celebrex capsule 200 mg, 1 capsule qd (AM before meal)
- Placebo (n=114): tablets and capsule

Rescue medications:

Dispensed at Screening (consented), at the Baseline Visit and Visit 4 (Week 6)

- Acetaminophen tablets: not to exceed 3 g/day and discontinued at least 48 hours before any WOMAC assessments
- Antacid tablets: not to exceed 6 tablets/day

Concomitant therapy:

The following medications were to have been allowed during the study:

- Low-dose aspirin (LDA, 325 mg/day or less) if started at least 4 weeks before Screening
- Anti-platelets medications (e.g., clopidogrel), but not if used concomitantly with aspirin
- Prednisone oral, up to 7.5 mg/day was allowed if the subject was on a stable dose for at least 12 weeks prior to the first dose of study medication.

- Inhaled steroids for asthma

The following medications were not to have been allowed during the study:

- Selective or non-selective NSAIDs, other than LDA during the treatment phase.
- Parenteral steroids
- Lithium
- Glucosamine and/or chondroitin sulfate
- Analgesics including narcotics and muscle relaxants at any time from Screening to the end of treatment
- PPI, H2 receptor antagonist or sucralfate or Cytotec® (misoprostol) from Screening through the end of treatment
- Anti-coagulants (eg, Coumadin®, warfarin, nutritional supplements having anticoagulant properties) from Screening to the end of treatment
- Other investigational drug(s) from 4 weeks prior to Screening to the end of treatment

Efficacy and Safety Assessments

Follow-up visits: as shown in the assessment flow chart (Table 1), there were to have been three in-treatment visits, at Weeks 1 (day 7), 6 and 12, for efficacy and safety assessments. The eDiary was used for inter-visit assessments.

Assessment administration were to have been completed in the morning, prior to the AM dose and with the exception of the MDHAQ, all were administered using the e-diaries enabled with touch screen technology and customized software. The MDHAQ was completed in paper format.

Table 1. Visit and Assessment Schedules
(From sponsor's Table 2 in the Study 307 report)

Weeks	Screening	OA Flare Determination	Baseline/ Randomization	Treatment			
	-1(-2)	7-14 Days after Screen	0	1 +/- 2 Days	6 +/- 3 Days	12 +/- 3 Days	
Visit	1		2	Day 1-6	3 Day 7	4	5
Informed consent	X						
In/exclusion criteria	X						
ECG	X						
Medical history	X		X				
Laboratory tests	X		X ¹	X	X	X	
Vital signs	X		X	X	X	X	
Physical examination	X						X
Urine Pregnancy test ²	X		X	X	X	X	
Dispense acetaminophen	X		X			X	
Randomization			X				
Dispense study drug			X			X	
Dispense/return e-diary			X				X
Dispense antacids			X			X	
Study drug and rescue med accountability						X	X
Prior and concomitant medications	X		X		X	X	X
Adverse events ³			X		X	X	X
WOMAC ^{4,5,6}	X ⁵	X ⁵	X ⁹	X ⁶	X ⁶	X	X
Heartburn assessment ^{4,7}			X	X	X	X	X
PGA (5-point Likert scale) ⁴	X	X	X ⁹	X	X		
PGA-VAS ⁴			X		X	X	X
APS-POQ ⁴			X	X	X		
mSODA ^{4,7}			X	X	X	X	X
MDHAQ			X		X	X	X
OMERACT-OARSI OA Responder Index						X	X
Subject study drug adherence ⁷				X	X	X	X
Subject rescue medication use ⁸				X	X	X	X

1 = Repeat laboratory tests at Baseline if > 14 days from Screening to Baseline

2 = Women of child-bearing potential

3 = Serious adverse events were captured from time of informed consent, non-serious adverse events from the time of first intake of study drug.

4 = Electronic efficacy assessments were completed in the morning prior to study drug dosing

5 = Question 1, WOMAC Pain Subscale (administered at Screening and at OA flare determination)

6 = WOMAC Pain Subscale only

7 = Completed daily using subject take-home e-diaries

8 = Completed as needed using subject take-home e-diaries

9 = PGA (Likert scale) and Question 1 of the WOMAC were transferred to the Baseline Visit in the e-diary once the subject had a qualifying OA flare.

Efficacy outcome measures:

- 1) WOMAC index at Baseline, Weeks 6 and 12 using a 48-hour recall on 100-mm VAS
- 2) WOMAC Pain on Days 1-7 using a 24-hour recall on 100-mm VAS
- 3) Modified Severity of Dyspepsia Assessment (mSODA): the 6-question instrument was daily self-administered to measure dyspepsia pain intensity, non-pain symptoms, and satisfaction with dyspepsia-related health, using a 24-hour recall (*on average* for 5 questions and *worst* for 1 question).
- 4) Heartburn: daily using 24-hour recall of burning feeling (from the stomach or lower part of the chest toward the neck) on scale “none, mild, moderate or severe”. The percent of days with resolution of heartburn was calculated for each subject.
- 5) Patient Global Assessment (PGA) of OA: 5-point scale at screening and on Days 1-7, VAS at Baseline and each subsequent visit
- 6) MDHAQ (Multi-Dimensional Health Assessment Questionnaire): the 10-question instrument was administered at the Baseline and subsequent visits to collect medical history in Physical Function, Pain, and Global Health Status.
- 7) APS-POQ (American Pain Society Patient Outcome Questionnaire): the 5-question instrument was administered at Baseline and on Days 1-7 (at home by eDiary) to measure the pain intensity and duration over a 7-day period.
Question 1: Have you experienced any pain in the last 24 hours? (yes or no)
Question 2: How much pain are you having now? (11-point scale)
Question 3: The worst pain in the last 24 hours? (11-point scale)
Question 4: Average pain in the last 24 hours? (11-point scale)
Question 5: How has pain interfered with you in the following areas? (11=point for each)
 - a. General Activity
 - b. Mood
 - c. Walking Ability
 - d. Relations With Other People
 - e. Sleep
 - f. Normal Work, Including Housework
 - g. Enjoyment of Life
 - h. Total
- 8) OMERACT-OARSI Responder Index: the composite of WOMAC and PGA-VAS at weeks 6 and 12 were used for a responder analysis.

Primary endpoint (three co-primary endpoints):

- 1) The mean change from Baseline in *WOMAC Pain* at Week 12
- 2) The mean change from Baseline in *WOMAC Function* at Week 12
- 3) The mean change from Baseline in *PGA-VAS* at Week 12

Secondary endpoints

- 1) Mean change from Baseline in the *mSODA average daily pain intensity* at Weeks 6 & 12
- 2) Pre-Specified NSAID-associated Upper Gastrointestinal Adverse Events (Table 2).
- 3) Time (in days) to first report of good or excellent response of PGA on Days 1-7
- 4) Mean change from Baseline in Total WOMAC score at Weeks 6 & 12
- 5) Mean change from Baseline in WOMAC Pain, Stiffness and Function scores at Week 6

- 6) Mean change from Baseline in PGA – VAS at Week 6
- 7) Percent of days with heartburn resolution at Weeks 6 & 12
- 8) Use of rescue medications (acetaminophen, supplemental antacid or any rescue medication during active treatment): proportion of subjects, percent of days, amount (number of tablets), time to first rescue acetaminophen for OA knee pain
- 9) Mean change from Baseline in MDHAQ (Function, Pain and Global Health Status) and overall score (Rheumatology Assessment of Patient Index Data, or RAPID-3) at Weeks 6 and 12
- 10) Mean change from Baseline in APS-POQ total score on Days 1-7
- 11) Mean change from Baseline in daily WOMAC Pain score on Days 1-7

Table 2. Pre-Specified NSAID-Associated Upper Gastrointestinal Adverse Events
(From sponsor’s Table 3 in the Study 307 report)

Preferred Term
Gastritis
Gastrointestinal hemorrhage
Duodenal ulcer*
Abdominal pain, upper
Dyspepsia
Nausea
Abdominal tenderness
Abdominal discomfort
Abdominal pain
Gastroesophageal reflux disease
Stomach discomfort
Vomiting
Hyperchlorhydria

Exploratory Endpoint:

OMERACT-OARSI responder index at Weeks 6 and 12

Safety Assessments:

- 1) Vital signs at all visits
- 2) Physical Examination at screening and discharge
- 3) 12-Lead Electrocardiogram at Screening
- 4) Clinical laboratory (blood chemistry and hematology) at Screening and all treatment visits
- 5) Adverse events during entire study
- 6) Pre-specified GI events (included in the Efficacy Assessment)

Statistical analyses:

Sample Size:

The sample size, n=570 (228 per active treatment and 114 for placebo) was estimated to sufficiently reject the null hypothesis using a 2.5% 1-sided test with 90% power, with NI margins of 10 mm on WOMAC Pain and Function Index (100-mm VAS) and the PGA (on 100-mm VAS) and with 10% dropouts. The sample size and power calculations were made under the assumption that non-inferiority would be tested with the expectation that the difference between PN400 and celecoxib would be 2 mm VAS in favor of celecoxib.

Analysis populations:

- Intent-to-treat (ITT) population (for primary analysis): all randomized subjects who received *at least 1 dose* of study drug and provided *at least 1 post-Baseline* efficacy evaluation.
- ITT without LOCF population: the ITT subjects who provided Week 12 (within the 12 Week analysis window per the Statistical Analysis Plan) WOMAC data [*as per the Applicant's response to the DAARP's requests on Dec 18, 2009*].
- Completer: subjects who have all scheduled visits through the Week 12 or final visit; not all completers necessarily provided Week 12 WOMAC data, thus "Completers" > "ITT without LOCF" [*as per the Applicant's response to the DAARP's requests on Dec 18, 2009*].
- Per-protocol (PP) population (for supportive analysis): all ITT subjects who did not violate the protocol in any major way that would have impacted the assessment of efficacy, and who had at least 70% overall treatment compliance.
- Safety population: all randomized subjects who received at least 1 dose of study drug.

Primary efficacy analysis:

- Non-inferiority (NI) in the co-primary endpoints between PN400 and celecoxib using analysis of covariance (ANCOVA) in ITT population with baseline score as covariate and treatment as the factor. The treatment difference between the two active groups was presented as *PN400 minus celecoxib*. A negative treatment difference in WOMAC endpoints favors PN400, and a positive treatment difference in the PGA-VAS endpoint favors PN400. The NI would be established based on the treatment differences:
 - if the *upper bound* of the 2-sided 95% CI was less than or equal to a NI margin of +10 mm for the WOMAC Pain and Function domains, and
 - if the *lower bound* of the 2-sided 95% CI was greater than or equal to a NI margin of -10 mm for PGA-VAS.
- Dropouts or missing data were imputed with a Last-Observation-Carried-Forward (LOCF) method. The subjects included in LOCF analysis at Weeks 6 and 12 are summarized in Table 3. In the primary efficacy analysis (see below), the Applicant actually used a "modified" ITT (at least one dose and at least one post-dose assessment).

Secondary efficacy analysis:

- Treatment differences in three co-primary endpoints from placebo were analyzed using 2-tailed F-test.

- The least-square estimates of the mean changes from Baseline and pair-wise differences from placebo (PN400 vs. placebo, celecoxib vs. placebo) were determined to support the use of the NI margin of 10 mm.
- Analysis in PP population with LOCF imputation.

Sensitivity analysis:

- Pre-specified analysis using ITT without LOCF imputation
- *Post-hoc* analyses requested by the Division (DAARP):
 - BOCF (Baseline-Observation-Carried-Forward): all missing data
 - BOCF-LOCF hybrid: BOCF for LOE and AEs; LOCF for others.
 - MMRM (Mixed-model Repeated-Measures): uses all data from all subjects who had baseline values and does not require any ad-hoc data imputation for missing data.

Table 3. ITT Population for primary analysis (LOCF imputation)
(From the Applicant’s unnumbered/untitled table in Page 54 of the Study 307 report)

	PN 400	Celecoxib	Placebo
Total ITT	246	242	124
WOMAC Pain and Function			
Subjects with no post-baseline value*	20	21	16
Subjects included in LOCF Analysis	226	221	108
Subjects with Week 12 value	187 (83 %)	179 (81 %)	84 (78 %)
Subjects with Week 6 value	39 (17 %)	42 (19 %)	24 (22 %)
PGA-VAS			
Subjects with no post-baseline value*	4	12	5
Subjects included in LOCF Analysis	242	230	119
Subjects with Week 12 value	192 (79 %)	180 (78 %)	87 (73 %)
Subjects with Week 6 value	50 (21 %)	50 (22 %)	32 (27 %)

* Excluded from Last Observation Carried Forward (LOCF) analysis

Amendments of protocol

The trial appears to have been conducted as originally designed (by following the original protocol) except with the following protocol amendments:

Amendment 1, dated 18 February 2008, prior to any subjects enrolling in the study:

- clarified footnotes for the schedule of events table, defined visit windows, revised and refined inclusion criteria, and specified randomization criteria.
- provided for upper and lower reference points for the pain scales on the APS-POQ sample questionnaire
- increased the number of sites
- changed the recall time for the heartburn question
- clarified rescue medication use and analysis

Amendment 2, dated 24 September 2008

- corrected minor administrative errors

- clarified rescue medication use and analysis
- clarified the statistical section
- upon request from FDA, changed the population for primary analysis from the PP to include the ITT population (see the FDA Meeting Minutes dated on June 24, 2008)

Changes in analysis plan

- low-dose aspirin use and smoking status were added to the subgroup analyses.
- subgroup analyses for the OMERACT-OARSI were not performed since these were exploratory.

RESULTS

Disposition of study subject:

Total enrollment: N= 619 subjects were enrolled from 75 study centers and randomized to the following three groups. Overall disposition of subjects was comparable across three groups (Table 4).

- n=248 to PN400
- n=247 to celecoxib
- n=124 to placebo

Approximately 99% (n=614) received ≥ 1 dose of study medication

Table 4. Disposition of study subjects
(From the sponsor’s Table 4 and Table 14.1.1 in the Study 307 report)

Randomized Population†	PN400 (500/20mg bid)	Celecoxib (200 mg qd)	Placebo	Total
	N=248	N=247	N=124	N=619
	n (%)	n (%)	n (%)	n (%)
Safety Population	247 (99.6)	243 (98.4)	124 (100)	614 (99.2)
ITT Population	246 (99.2)	242 (98.0)	124 (100)	612 (98.9)
PP Population	232 (93.5)	219 (88.7)	113 (91.1)	564 (91.1)
Completed Study	208 (83.9)	208 (84.2)	105 (84.7)	521 (84.2)
Dropouts	40 (16.1)	39 (15.8)	19 (15.3)	98 (15.8)

† Definition of populations as pre-specified in the protocol and in the study report:
 - Safety population: subjects with ≥ 1 dose
 - Intent-to-Treat (ITT) Population: subjects with ≥ 1 dose and ≥ 1 post-baseline efficacy measure
 - Per-protocol (PP) population: IIT subjects without major protocol violation

Dropouts: overall dropout rate was 16% (n=98) and comparable across three groups. The most common reasons for dropouts were AEs, followed by “withdrew consent” and “other”. In the Applicant’s report, “Lack of Efficacy” were not stratified but included in “Withdrew Consent” and “Others”. As per the statistical reviewer (Ms. Katherine Meaker), the dropouts due to “Lack of Efficacy” were classified in the sensitivity analyses such as BOCF/LOCF.

The following are reasons for the dropouts re-calculated from the Applicant’s dataset “ADSL” (Table 5):

- Adverse events: n=42 (6.8%)
- Withdraw consent: n=25 (4.0%)
- Lack of efficacy: n=16 (2.6%)
- Lost to follow-up: n=2 (0.3%)
- Other: n=25 (4.0%) (noncompliance, travel/job, concomitant medications)

Table 5. Reasons for dropouts in Study 307
(Calculated from the Applicant’s dataset ADSL – Subject Level Analysis Dataset)

Reason for Dropout	PN400 (500/20mg bid)	Celecoxib (200 mg qd)	Placebo	Total
	N=248	N=247	N=124	N=619
	n (%)	n (%)	n (%)	n (%)
Total	40 (16.1)	39 (15.8)	19 (15.3)	98 (15.8)
Adverse Event	19 (7.7)	16 (6.5)	7 (5.6)	42 (6.8)
Lack of efficacy	6 (2.4)	4 (1.6)	6 (4.8)	16 (2.6)
Withdrew Consent	9 (3.6)	12 (4.9)	4 (3.2)	25 (4.0)
Lost to Follow-up	0	2 (0.8)	0	2 (0.3)
Other	8 (3.2)	5 (2.0)	2 (1.6)	15 (2.4)

Demographic characteristics

Demographics of the ITT population appeared comparable across three groups:

- 64% females: slightly fewer females in celecoxib group
- 80% white and 15% black
- Mean age of 62 years (49-90): slightly more subjects aged ≥ 65 years)
- Mean BMI of 33 kg/m²
- 85% non-smokers: slightly more smokers in placebo

Baseline characteristics

The baseline characteristics in the ITT population and PP population were generally comparable across three groups:

- All subjects met ACR criteria and ACR functional class for OA of the knee.
- Past and current medical conditions: All subjects had current co-morbid. Most common current conditions were in musculoskeletal, cardiovascular and endocrine/metabolic systems. GI disorders were about 48% (and 30% in past), which was comparable across groups.
- Prior medications were generally balanced across groups:
 - More than 93% of subject took NSAIDs (36% on ibuprofen, 28% on naproxen, 15% on celecoxib, and 14% others including meloxicam, diclofenac, nabumetone and piroxicam) (Table 6)

- Approximately 23% of subjects took low-dose aspirin.
- More than 60% of subjects took anti-hypertensive medications with slightly more subjects in the PN400 group (67% in PN400, 63% in celecoxib and 60% in placebo)

Table 6. Previous use of analgesics
(From the Applicant’s Table 14.1.9.1 in Study 307)

Analgesics	PN400 (N=246)	Celecoxib (N=242)	Placebo (N=124)	Total (N=612)
	n (%)	n (%)	n (%)	n (%)
Ibuprofen	83 (33.7%)	81 (33.5%)	55 (44.4%)	219 (35.8%)
Naproxen	69 (28.0%)	75 (31.0%)	27 (21.8%)	171 (27.9%)
APAP	56 (22.8%)	53 (21.9%)	28 (22.6%)	137 (22.4%)
Celecoxib	40 (16.3%)	37 (15.3%)	18 (14.5%)	95 (15.5%)
Opioids (combo)	11 (4.5%)	18 (7.4%)	4 (3.2%)	33 (5.4%)

Protocol deviations:

A total of seven subjects failed to meet subject selection criteria:

- N=4 on PN400 (3 to Exclusion and 1 to Inclusion)
- N=1 on placebo (Exclusion)
- N=2 on celecoxib (1 each to Exclusion and Inclusion)

Major protocol violations:

The PP population excluded 16 subjects (6%) from the PN400 group and 28 (11%) subjects from the celecoxib group and 11 subjects (9%) from the placebo group (Table 7).

Table 7. Major Protocol Violations and Exclusions from PP Analyses
(From the sponsor’s Table 5 in the Study 307 report)

	PN 400 bid N=248	Celecoxib 200 qd N=247	Placebo N=124
	n	n	n
Noncompliance	13	17	7
Disallowed Medication Used	1	5	4
Did Not Take Any Study Medication	1	4	0
No Post-baseline Efficacy Evaluations	1	1	0
OA Flare Criteria Not Met	0	1	0

Treatment compliance

Treatment compliance was measured as per protocol:

- Per subject for each visit: the number of doses taken divided by the number of doses scheduled to be taken between visits.
- Per subject during the double-blind period: the total number of doses taken divided by the total number of doses scheduled to be taken during the double-blind study period; 70% was as a compliance cut-off.

Approximately 93% of subjects had $\geq 70\%$ overall compliance and was comparable across three groups (94% in PN400, 92% in Celecoxib and 94% in placebo).

Primary analysis of primary endpoints

The Applicant's ITT/LOCF analysis of three co-primary endpoints showed that PN400 was non-inferior to celecoxib and both active treatments were superior to placebo (Table 8):

- PN400 met the pre-specified NI margin compared to celecoxib in three co-primary endpoints:
 - The upper bound of 95% CI was ≤ 10 mm for WOMAC Pain (4.32) and WOMAC Function (4.38)
 - The lower bound of 95% CI was ≥ -10 mm for PGA-VAS (-5.08)
- Both active treatments were statistically superior to placebo in the three co-primary endpoints. The treatment size of PN400 was slightly larger than celecoxib in WOMAC Pain and Function but not PGA.

Sensitivity analysis of primary endpoints:

- **Pre-specified sensitivity analysis** – analysis in the ITT population without LOCF imputation (ITT without LOCF) was a pre-specified analysis in SAP. The NI results of three co-primary endpoints (Table 9) were consistent with those from the primary analysis.
- **Post-hoc sensitivity analyses:** The results from the three post-hoc sensitivity analyses (BOCF, LOCF/BOCF hybrid and MMRM) were submitted in ISE (Section 2.2.5):
 - Differences (about 5 mm) between PN400 and celecoxib were within the pre-specified NI margin for all three co-primary endpoints (Table 10)
 - Both PN400 and celecoxib were statistically superior to placebo (Table 11) in three co-primary endpoints with all three sensitivity analyses.

Table 8. Primary Analysis of Non-inferiority (vs. Celecoxib) and Superiority (vs. Placebo) in ITT population with LOCF imputation

(From the Applicant's Tables 8, 9, 10 and 12 in Study 307)

Three Co-primary Endpoints*	PN400 N=246	Celecoxib N=242	Placebo N=124	PN400 minus Celecoxib	Differences from Placebo	
					PN400	Celecoxib
WOMAC Pain						
n	226	221	108			
Baseline Mean (SD)	71.9 (17.1)	68.3 (17.7)	66.5 (19.1)			
LS Mean	-41.99	-41.77	-35.64	-0.22	-6.36	-6.14
95% CI				(-4.76, 4.32)	(-11.98, -0.73)	(-11.75, -0.52)
p-value					P=0.027	P=0.032
WOMAC Function						
n	226	221	108			
Baseline Mean (SD)	68.7 (19.8)	66.0 (19.9)	63.5 (20.5)			
LS Mean	-36.38	-36.29	-28.9	-0.09	-5.78	-5.68
95% CI				(-4.57, 4.38)	(-11.32, -0.23)	(-11.23, -0.14)
p-value					P=0.041	P=0.045
PGA-VAS						
n	242	230	119			
Baseline Mean (SD)	32.3 (22.3)	31.8 (20.5)	35.3 (22.9)			
LS Mean	21.17	21.64	14.41	-0.47	6.76	7.23
95% CI				(-5.08, 4.14)	(1.14, 12.37)	(1.56, 12.89)
p-value					P=0.018	P=0.013

* Least Square (LS) mean changes from baseline at Week 12 and the 95% CI were calculated with ANCOVA using baseline as a continuous covariate. A negative change in the WOMAC Pain and Function and a positive change in the PGA-VAS indicate improvement.

Table 9. Sensitivity analysis of non-inferiority in ITT/without LOCF
(From the Applicant’s Table 14.2.3 of Study 307 report)

Three Co-primary Endpoints*	PN400 N=232	Celecoxib N=219	PN400 minus Celecoxib
WOMAC Pain: n	187	179	
LS Mean	-44.65	-43.20	-1.45
95% CI			(-6.16, 3.25)
WOMAC Function: n	187	179	
LS Mean	-38.94	-37.86	-1.08
95% CI			(-5.77, 3.61)
PGA-VAS: n	192	180	
LS Mean	23.35	23.19	0.16
95% CI			(-5.05, 5.37)

Note: See Table 8

Table 10. Post-hoc sensitivity testing of primary non-inferiority analysis
(From the Applicant’s Table 5.35.3.1.24 in ISE, p78, for Study 307)

	WOMAC Pain (95% CI)	WOMAC Function (95% CI)	PGA-VAS (95% CI)
LOCF per SAP Sensitivity Analysis	-0.22 (-4.76, 4.32)	-0.09 (-4.57, 4.38)	-0.47 (-5.08, 4.14)
BOCF	-2.01 (-7.02, 2.99)	-1.67 (-6.39, 3.06)	1.6 (-2.94, 6.14)
Hybrid BOCF- LOCF	-0.64 (-5.46, 4.19)	-0.73 (-5.35, 3.88)	1.11 (-3.44, 5.66)
MMRM	-0.28 (-2.80, 2.24)	-0.29 (-2.83, 2.24)	0.84 (-1.73, 3.41)

Source: PN400-307 Table 14.2.1, Table E2.24, Table E2.25, Table E2.26

Data represented the differences in the LS Mean change from baseline at Week 12 between PN400 and celecoxib, and 95% CI of the difference.

Table 11. Post-hoc sensitivity testing of primary superiority analysis
(From the Applicant’s Table 5.35.3.1.26 in ISE, p79 for Study 307)

	WOMAC Pain		WOMAC Function		PGA-VAS	
	Diff.	p-value	Diff.	p-value	Diff.	p-value
LOCF per SAP						
PN 400 - Placebo	-6.36	0.0268	-5.78	0.0412	6.76	0.0184
Celecoxib - Placebo	-6.14	0.0322	-5.68	0.0447	7.23	0.0125
Sensitivity Analysis						
BOCF						
PN 400 - Placebo	-8.29	0.0076	-7.59	0.0097	8.65	0.0022
Celecoxib - Placebo	-6.28	0.0429	-5.92	0.0439	7.04	0.0129
Hybrid BOCF- LOCF						
PN 400 - Placebo	-7.29	0.0148	-7.10	0.0132	8.14	0.0039
Celecoxib - Placebo	-6.65	0.0261	-6.37	0.0265	7.03	0.0132
MMRM						
PN 400 - Placebo	-4.63	0.0034	-3.82	0.0162	4.63	0.0040
Celecoxib - Placebo	-4.35	0.0059	-3.52	0.0268	3.79	0.0193

Source: PN400-307 Table 14.2.5.1, Table E2.27, Table E2.28, Table E2.29

Data represented the differences in the LS Mean change from baseline at Week 12 between active and placebo.

Secondary analyses of primary endpoints:

PP/LOCF analysis (Table 12):

- PN400 was not noninferior to celecoxib for the three co-primary endpoints. The differences in WOMAC Pain and Function between PN400 and celecoxib were numerically larger with the PP analysis than with the ITT analysis (favorable to PN400, suggesting PP analysis is more sensitive).
- However, unlike results from the primary analysis both PN400 and celecoxib were not statistically superior to placebo in WOMAC Pain and WOMAC Function except PAG. [See the Discussion for

Comparison of effect size:

- With the ITT/LOCF analyses, the effect sizes (active vs. placebo) were comparable between PN400 and celecoxib in three co-primary endpoints (Table 8).
- However with the PP/LOCF analyses, the effect sizes are not comparable between PN400 and celecoxib because both were not statistically superior to placebo in WOMAC Pain and Function (Table 12).

Table 12. Non-inferiority and superiority Analyses in PP population with LOCF imputation
(From the Applicant’s Table 11 and Table 14.2.5.2 of Study 307 Report)

Three Co-primary Endpoints*	PN400 N=232	Celecoxib N=219	Placebo N=113	PN400 minus Celecoxib	Differences from placebo	
					PN400	Celecoxib
WOMAC Pain						
n	219	208	100			
LS Mean	-42.7	-41.47	-37.12	-1.23	-5.58	-4.35
95% CI				(-5.84, 3.38)	(-11.34, 0.19) P=0.058	(-10.13, 1.43) P=0.14
WOMAC Function						
n	219	208	100			
LS Mean	-37.17	-36.28	-31.68	-0.89	-5.49	-4.60
95% CI				(-5.46, 3.68)	(-11.20, 0.23) P=0.06	(-10.34, 1.15) P=0.116
PGA-VAS						
n	231	212	111			
LS Mean	21.80	22.03	15.81	-0.22	5.99	6.22
95% CI				(-4.99, 4.55)	(0.20, 11.79) P=0.043	(0.33, 12.10) P=0.038

* See Table 8

Verification by the statistical reviewer (Ms. Katherine Meaker): The Applicant’s analyses were verifiable. However, the non-inferiority of PN400 over celecoxib can not be established because the Applicant’s pre-specified NI margin (10 mm) was inadequate based on the observed effect size of celecoxib over placebo from this study. The re-analyses using the newly-defined NI

margin computed from the effect size show that PN400 is not non-inferior to celecoxib. See the statistical review for details.

Secondary efficacy endpoints

1) *WOMAC Index and PGA at Week 6*

The LS mean changes from baseline at week 6 in the three co-primary efficacy variables according to the Applicant's ITT/LOCF analysis are shown (see the Applicant's Table 14.2.10):

- WOMAC Pain (Figure 1):
 - There were no significant differences (numerically almost same) between PN400 and celecoxib (-39.31 vs. -40.25)
 - Both PN400 and celecoxib were superior to placebo (9% CI did not cross "0"). The data at Week 1 were from Day 7 of Figure 6.
- WOMAC Function (Figure 2):
 - PN400 showed slightly less effects than celecoxib (-33.81 vs. -34.69) without statistical significance
 - Both PN400 and celecoxib were numerically better than placebo.
- WOMAC Stiffness (Figure 3):
 - PN400 showed slightly less effects than celecoxib (-35.62 vs. -38.37) without statistical significance
 - Both active treatments showed improvement relative to placebo without statistical significance for PN400.
- WOMAC Total score (Figure 4):
 - PN400 showed similar effects to celecoxib (-36.39 vs. -37.69) without statistical significance.
 - Both active treatments were statistically superior to placebo.
- PGA on 100-mm VAS (Figure 5):
 - PN40 was slightly better than celecoxib (22.62 vs. 19.99)
 - Both PN400 and celecoxib showed improvement relative to placebo with statistical significance for PN400

Figure 1. LS Mean Change in WOMAC Pain from baseline at Weeks 1, 6 and 12
(From the Applicant's Table 14.2.13.1, Table 14.2.10 and Table 14.2.5.1 in Study 307 report)

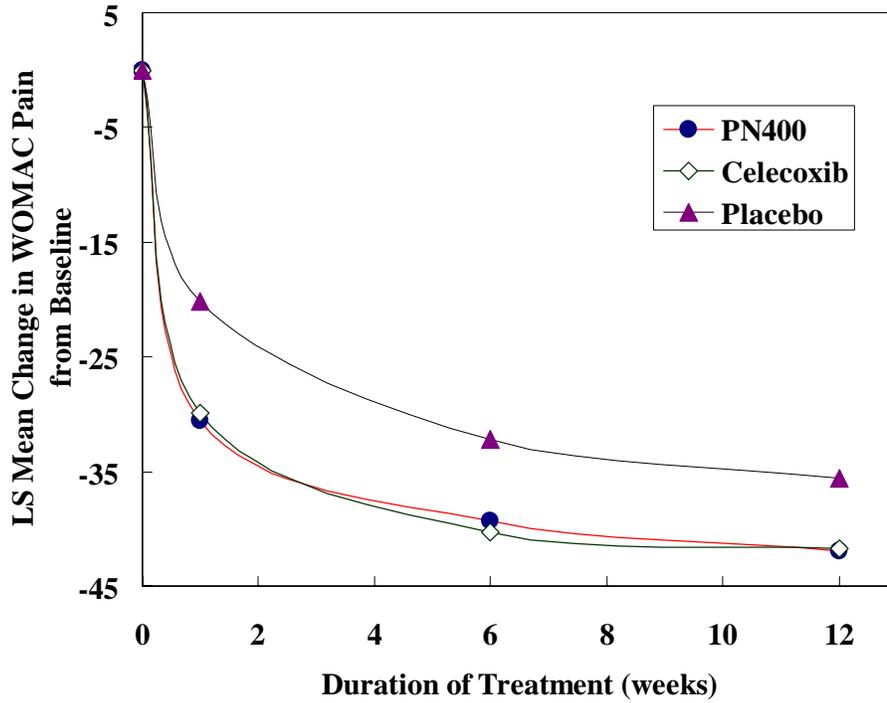


Figure 2. LS Mean Change in WOMAC Function from baseline at Weeks 6 and 12
(From the Applicant's Table 14.2.10 and Table 14.2.5.1 in Study 307 report)

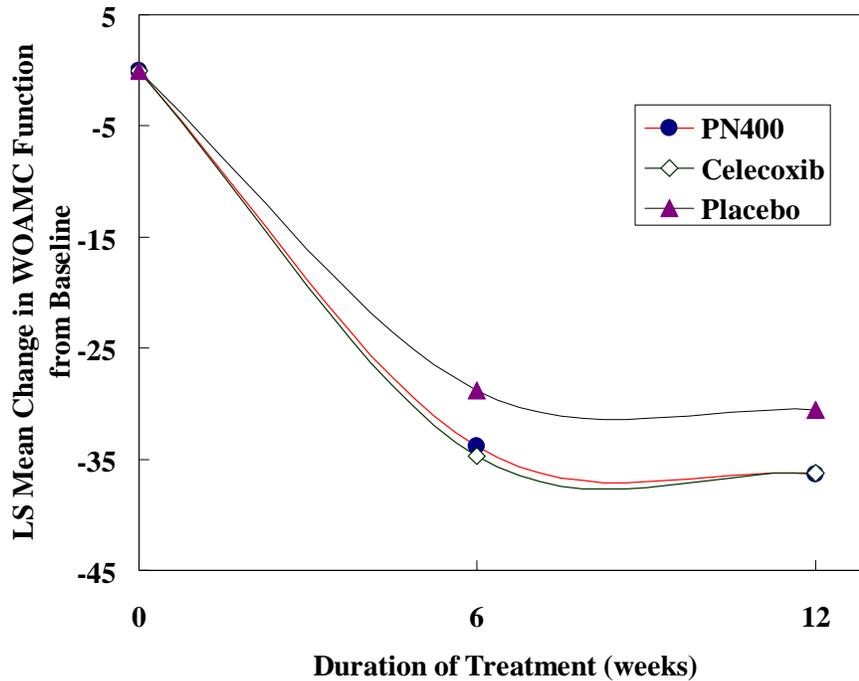


Figure 3. LS Mean Change in WOMAC Stiffness from baseline at Weeks 6 and 12
(From the Applicant's Table 14.2.10 and Table 14.2.5.1 in Study 307 report)

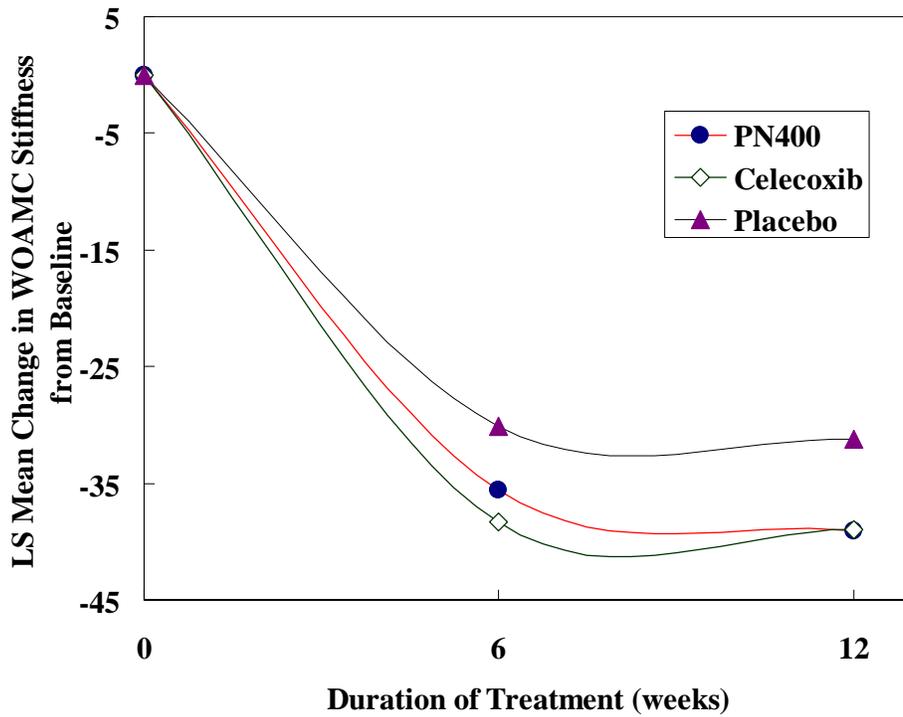


Figure 4. LS Mean Change in WOMAC Total score from baseline at Weeks 6 and 12
(From the Applicant's Table 14.2.9 in Study 307 report)

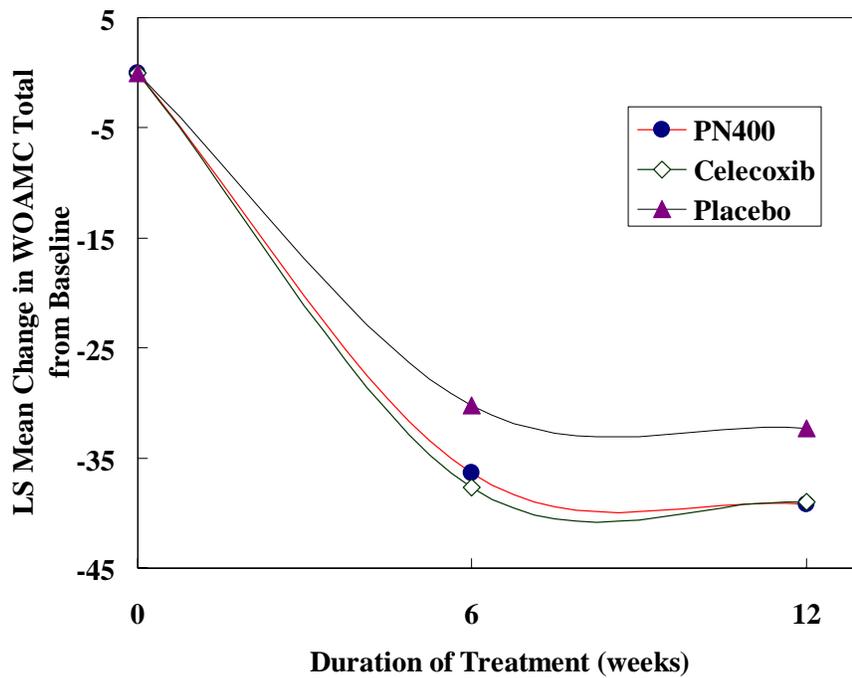
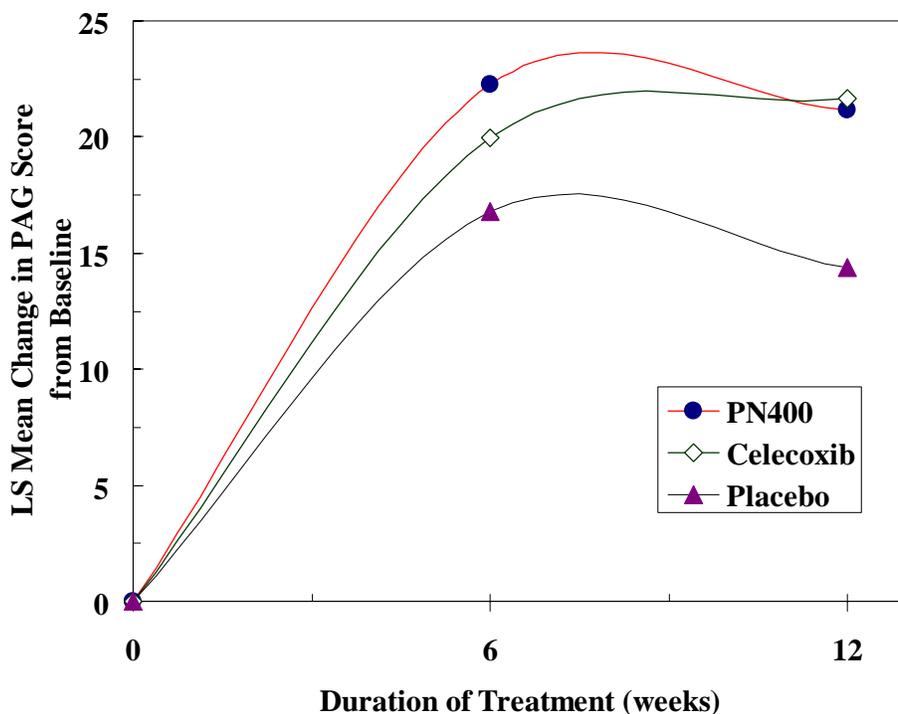


Figure 5. LS Mean Change in PAG-VAS from baseline at Weeks 6 and 12

(From the Applicant's Table 14.2.10 and Table 14.2.5.1 in Study 307 report)



2) WOMAC Stiffness and Total at Week 12

The LS mean changes from baseline at Week 12 according to the Applicant's ITT/LOCF analysis (see Applicant's Table 14.2.9):

- WOMAC Stiffness (Figure 3):
 - PN400 showed slightly less effects than celecoxib (-39.09 vs. 38.97) without statistical significance
 - Both active treatments showed improvement relative to placebo with statistical significance.
- WOMAC Total score (Figure 4):
 - PN400 showed similar effects to celecoxib (-39.23 vs. 38.99) without statistical significance.
 - Both active treatments were statistically superior to placebo.

3) WOMAC Pain on Days 1-7

The LS mean changes from baseline in WOMAC Pain (*average daily pain scores*) at Days 1-7 according to the Applicant's ITT/LOCF analysis are shown in Figure 6 (also see the Applicant's Table 14.2.13.1):

- PN400 was slightly less than celecoxib at Days 3-7 without statistically significance.
- Both active treatments were superior to placebo with statistical significance at Day 2-7.

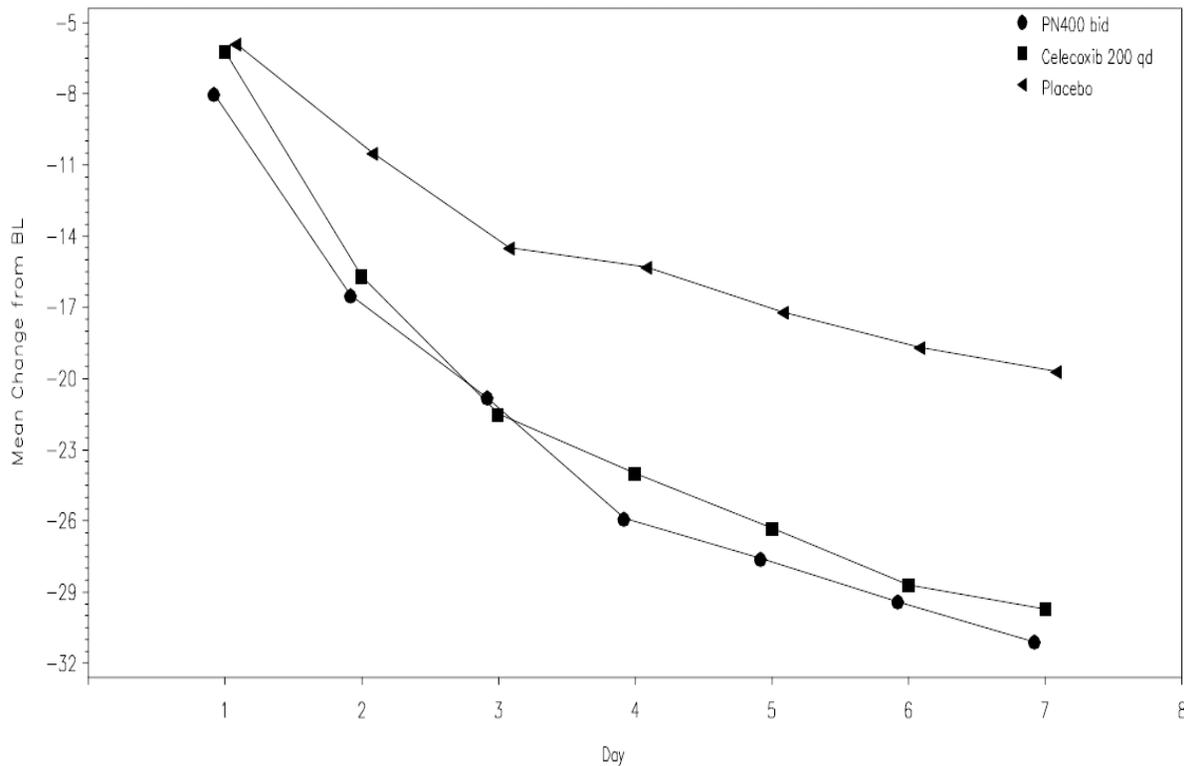
Table 13. Time to the first response in PGA during the Days 1-7 in the ITT population
(From the Applicant’s Table 14.2.8.1 of the Study 307 report)

	PN400 N=246	Celecoxib N=242	Placebo N=124	PN400 vs. Celecoxib
Responders				
n (%)	134 (54.5%)	123 (50.8%)	55 (44.4%)	
95% CI	(48.2%, 60.7%)	(44.5%, 57.1%)	(35.6%, 53.1%)	
Time to Response				
Median (Days)	6.0	6.0	-	0.0
95% CI	(5.0, 7.0)	(5.0, -)		(-1.9, 1.9)
p-Value*	0.1032	0.2794		

Time to response was based on Kaplan-Meier estimate

* A log-rank test of the difference in time-to-response curves compared to placebo

Figure 6. Mean Change in WOMAC Pain from baseline during Days 1-7
(From the Applicant’s Figure 14.2.13.2 in the Study 307 report)



4) APS-POQ on Days 1-7

The American Pain Society -- Patient Outcome Questionnaire (APS-POQ) questionnaire was administered daily for the first 7 days (Days 1-7).

- Questions 1-4 (pain *now*, *worst* and *average*)
 - PN400 was similar to celecoxib from day 1
 - Both active treatments were superior to placebo from day 2
- Question 5 (pain *interfered with activities*): overall on each day after Day 1
 - PN400 was similar to celecoxib
 - Both active treatments were significant differences over placebo

5) MDHAQ (Multi-dimensional Health Assessment Questionnaire)

LS mean changes from baseline at weeks 6 and 12 in MDHAQ Physical Function, Pain and Global Health Status scores and overall scores (RAPID-3: Rheumatology Assessment of Patient Index Data) showed according to the Applicant's ITT/LOCF analysis (see Applicant's Table 14.2.11):

- PN400 was comparable to celecoxib without statistically differences.
- Both active treatments were statistically superior to placebo
- The overall improvement at Week 12 was slightly greater than at week 6.

6) Time to First Response in PGA

Daily response ("good" or "excellent") on PGA-Likert scale was assessed during Days 1-7, as shown in Table 13:

- Median time to the first response was 6 days for both PN400 and celecoxib treatment groups and >7 days for placebo. The differences between the active treatment and placebo were not statistically significant.
- The proportion of subjects with the response (responders) was comparable between PN400 and celecoxib; slightly more subjects in both treatment groups than in placebo reported "good" or "excellent" responses but with overlapped 95% CIs.

7) Rescue Acetaminophen (Table 14):

- Percent of subjects used ≥ 1 dose of acetaminophen was slightly lower with PN400 and celecoxib than placebo (73%, 72% vs. 80%)
- Mean total number of tablets was lower with PN400 and celecoxib than placebo (52, 51 vs. 69) with statistically difference; the mean number of tablets per subject per month was slightly lower with active treatments than placebo with statistically significant difference between PN400 and placebo.
- Mean time to first dose was 1 day with PN400 and 2 days with celecoxib and placebo (Table 14.2.16.1). The mean percent of days using acetaminophen was 42% with PN400, 39% with celecoxib, and 55% with placebo.

Table 14. Rescue use of acetaminophen and antacid in ITT population
(From the Applicant’s Table 16 in Study 307 report)

	PN 400 bid N=246	Celecoxib 200 qd N=242	Placebo (N=124)	PN 400 bid minus Celecoxib	PN 400 bid minus Placebo	Celecoxib 200 qd minus Placebo
Acetaminophen Rescue						
Time to First Rescue (Days)						
Median	1.0	2.0	2.0			
95% CI	1.0, 2.0	1.0, 2.0	1.0, 2.0			
Percent of Days Rescue was Used	42.3	38.8	55.4			
Tablets used per subject per month						
N	233	228	117			
Mean (SD)	21.0 (25.5)	23.1 (32.3)	28.7 (25.8)	-2.1	-7.7	-5.7
95% CI				(-7.4, 3.3)	(-13.5, -2.0)	(-12.5, 1.1)
Antacid Rescue						
Time to First Rescue (Days)						
Median	5.0	5.0	4.0			
95% CI	3.0, 8.0	3.0, 6.0	3.0, 8.0			
Percent of Days Rescue was Used	19.5	28.1	37.8			
Tablets used per subject per month						
N	238	236	119			
Mean (SD)	9.3 (17.5)	13.9 (21.6)	15.4 (37.6)	-4.6	-6.1	-1.4
95% CI				(-8.2, -1.1)	(-11.8, -0.3)	(-7.6, 4.7)

Source: Tables 14.2.16.1, 14.2.16.2

CI = confidence interval; SD = standard deviation.

8) OMERACT-OARSI

OMERACT-OARSI (Outcomes Measures in Arthritis Clinical Trials – Osteoarthritis Research Society International) was proposed as an exploratory analysis. The percent of subjects who met the OMERACT-OARSI criteria was greater with PN400 than celecoxib and placebo at both Week 6 (74%, 69% and 62%) and Week 12 (78%, 74% and 70%). The statistical significant difference was only shown between PN400 and placebo.

Concomitant Medications

Approximately 92% of subjects had concomitant medications during the study; the most commonly used medications were lipid modifying agents followed by multivitamin and antithrombotic agents. The types and quantities of the medications were comparable across three groups.

The concomitant analgesics and GI agents were rarely used during the study (across PN400, celecoxib and placebo groups):

- Drugs for peptic ulcer and GERD: 1.5% (n=9) (0.4%, 2.1% and 2.4%)
- Opioids: 2.4% (n=15) (2%, 2.5% and 3.2%)
- Other NSAIDs: 2.4 % (n=15) (2%, 1.2% and 5.6%)
- Other analgesics: 2% (n=12) (2.4%, 1.6% and 1.6%)

GI tolerability:

Evaluation of the GI tolerability to the treatments included *mSODA*, *heartburn-free days*, *pre-specified NSAID-associated events*, *rescues antacid use* and *treatment-emergent GI events* during the study. Overall, subjects treated with PN400 had similar or slightly better GI tolerability compared to celecoxib and placebo (Table 15).

More than 93% of subjects took NSAIDs (mostly ibuprofen, naproxen or celecoxib) prior to the study, which was comparable across three groups, see the above Baseline Characteristic for details). Therefore, a high event rate of NSAID-associated GI disorders should be expected at baseline in the study population. However, the detailed baseline GI event rates across three groups were reported in the study.

Table 15. GI tolerability assessment

(From the Applicant’s Tables 13, 15, 20, 14.3.3.1 and 14.2.16.2 in Study 307)

GI tolerability measures	PN400 N=245	Celecoxib N=237	Placebo N=123
mSODA (LS Mean)*	-3.79	-4.57	-3.73
Heartburn-free days (LS Mean)	78.9%	71.5%	66.1%
Pre-specified NSAID-associated events (incidence)	16.6%	16.9%	19.4%
Rescue antacid use (% subjects)	43%	55%	49%
Treatment-emergent GI events (% safety population)#	26.3%	23.0%	22.6%

* LS Mean Change in the modified severity of dyspepsia assessment (mSODA) from baseline at Week 12.

The incidence was calculated based on the Safety Population.

Modified SODA (mSODA):

The mean changes from baseline in the *average daily abdominal pain score* of mSODA (Modified Severity of Dyspepsia Assessment) at weeks 6 and 12 showed improvement across three groups compared to baseline. There were no differences in the changes from baseline at both time points between PN400 and placebo. PN400 treatment had less improvement than celecoxib at both time points without a statistical significance at Week 12 (Table 16) and unknown statistical significance at Week 6 (clearly PN400 had less improvement at Week 6 than celecoxib). At least numerically, subjects in the PN400 group experienced greater severity of dyspepsia than celecoxib at both time-points.

Table 16. mSODA Avery Daily Pain Sore in ITT population with LOCF
(From the Applicant’s Tables 13 and 14 in the Study 307 report)

Time Point	PN400 N=245	Celecoxib N=237	Placebo N=123	PN400 minus Celecoxib
Baseline				
Mean (SD)	10.9 (10.8)	11.8 (10.8)	11.9 (11.2)	
Week 6 Change from Baseline				
Mean (SD)	-3.2 (9.2)	-4.4 (8.9)	-3.7 (9.2)	
Week 12 Change from Baseline				
LS Mean	-3.79	-4.57	-3.73	0.77
95% CI				(-0.36, 1.91) p=0.183

mSODA: Modified Severity of Dyspepsia Assessment. The data represented the mean changes from baseline at Week 6 (arithmetic mean) and Week 12 (LS Mean). The higher the negative value means the less the severity of dyspepsia. The differences between PN400 and celecoxib at Week 6 were not reported in the study.

Subgroup analysis of mSODA by low-dose aspirin use showed that PN40 was numerically better than celecoxib and placebo in the aspirin users (23% subjects in total) but statistically worse than celecoxib in the non-aspirin users (Table 17).

Table 17. Subgroup analysis of mSODA by low-dose aspirin use in ITT/LOCF
(From Applicant’s Table 14.2.7.1 in Study 307)

Aspirin use	PN400 N=245	Celecoxib N=237	Placebo N=123
<i>Aspirin users</i>			
n	57	58	28
LS mean	-5.13†	-3.93	-4.08
<i>Non-Aspirin users</i>			
n	188	179	95
LS mean	-3.39‡	-4.78	-3.61

Least square mean change in mSODA average daily pain scores from baseline at Week 12. †p=0.355 and ‡p=0.033 between PN400 and celecoxib by ANCOVA; no statistical analyses available for the differences between active treatments and placebo.

Heartburn Resolution:

The percent of days (LS Mean) with no heartburn was significantly greater in subjects treated with PN400 (78.9%) than with celecoxib (71.5%) and placebo (66.1%) at Week 12 (Table 18); there was no significant difference between celecoxib and placebo. The similar trends in the heartburn-free days at Week 6 were reported. However, data on the percent of subjects experienced heartburn during the study were not reported in the study.

Table 18. Percent of Days without Heartburn in ITT Population
(From the Applicant's Table 15 in Study 307)

	PN 400 bid N=246	Celecoxib 200 qd N=242	Placebo N=124	PN 400 bid minus Celecoxib 200 qd	PN 400 bid minus Placebo	Celecoxib 200 qd minus Placebo
Baseline to Week 6						
N	245	241	123			
Mean (SD)	83.8 (29.3)	75.5 (34.0)	67.1 (37.2)			
Baseline to Week 12						
N	245	241	123			
Mean (SD)	83.9 (29.8)	75.8 (34.1)	68.5 (37.0)	8.2	15.4	7.3
ANCOVA						
LS Mean	78.9	71.5	66.1	7.4	12.8	5.4
95% CI				(2.10, 12.65)	(6.40, 19.24)	(-1.01, 11.89)

Source: [Table 14.2.15](#)

ANCOVA = analysis of variance; CI = confidence interval; LS = least squares; Max. = maximum; Min. = minimum; SD = standard deviation

NSAID-associated UGI AEs:

The percent of subjects experiencing the pre-specified NSAID-associated UGI adverse events, including duodenal ulcers, was similar across three groups:

- n=41 (16.6%) on PN400
- n=41 (16.9%) on celecoxib
- n=24 (19.4%) on placebo

The discontinuation rate due to pre-specified NSAID-associated UGI AEs was also similar across treatment groups with an overall rate of 1.6%.

Rescue Antacid (see above Table 14):

- Percent of subjects used antacid for dyspepsia was lower with PN400 (43%) than with celecoxib group (55%) and placebo (49%). The differences between PN400, but not celecoxib, and placebo were statistically significant.
- Mean total number of tablets taken per subject was lower with PN400 (24) than celecoxib or placebo (32 for both). Differences in the mean total number of antacid tablets between PN400 and celecoxib were significant. The mean number of tablets per subject per month was lower with PN400 than celecoxib and placebo with statistically significance.
- Median time to first antacid use was one day longer with PN400 and celecoxib (5 days) than placebo (4 days). The mean percent of days antacid was used was 20% with PN400, 28% with celecoxib, and 38% with placebo.

Safety evaluation

Extent of exposure

- Overall exposure to the study medication was similar across three groups.
- The mean duration of exposure in three groups was approximately 79±21 days in the safety population (n=614).
- The mean number of tablets and capsules taken per subject and per month were comparable between PN400 and celecoxib, and slightly lower in the placebo group.

Serious AEs: There were no deaths reported during the study. Ten subjects (2%) experienced SAEs. The causality can not be determined because most events were confounded by concomitant medical history (although the investigators concluded the “unrelated to study medication” for all SAEs except the acute anaphylaxis in the celecoxib group).

- PN400: n=5
 - incarcerated hernia (previous colon resection)
 - worsening knee OA
 - appendicitis (rupture)
 - stroke
 - acute pancreatitis
- Celecoxib: n=5
 - Chest/left shoulder pain (negative cardiac tests)
 - Chest pain (negative cardiac tests)
 - Acute anaphylaxis (*possibly related to study medication* as per the investigator)
 - Gangrene of right great toe and swelling of left supraclavicular area
 - Motor vehicle accident
- Placebo: n=0

AE-related dropouts: Approximately 6-7% of subject dropped out from the study due to AEs (mostly due to GI disorders):

- PN400: n=18 (7.3%)
- Celecoxib: n=16 (6.6%)
- Placebo: n=7 (5.6%)

Treatment-emergent AEs:

- The overall incidence of AEs was 50%, with slower lower rate in the celecoxib group (45% vs. 52% in PN400 and placebo). The majority of the AEs were mild or moderate, and 5-6% of subjects had severe AEs across all groups.
- The most common AEs were GI events (dyspepsia, diarrhea, nausea, upper abdominal pain) with a similar frequency in three groups:
 - PN400: 26%
 - Celecoxib: 23%
 - Placebo: 23%.
- Other AEs (non-GI) occurring at ≥ 2% in active treatment groups and greater than the occurrence rate in the placebo group were
 - Headache: 2.8% for PN400, 4.1% for celecoxib and 4.0% for placebo

- peripheral edema: 3.6% for PN400, 1.2% for celecoxib and 0.8% for placebo

SUMMARY

Efficacy:

This was a 12-week, randomized, double-blind, placebo-/active-controlled, non-inferiority trial for the indication “treatment of signs and symptoms of OA”. The study subjects were patients with OA of the knee and were randomized at a ratio of 2:2:1 to PN400 bid (n= 246), celecoxib 200 mg qd (n=242) or placebo (n=124). Duration of the treatment was 12 weeks.

The standard three co-primary endpoints (mean change from baseline at week 12 in WOMAC Pain, WOMAC Function and PGA) were used to establish non-inferiority of PN400 over celecoxib and superiority of the active treatments (PN400 and celecoxib over placebo). The NI margin was pre-specified as 10 mm difference (2-sided 95% CI) from celecoxib.

The primary analysis was ANCOVA in the ITT population with LOCF imputation for dropouts (dropout rate of 16%, comparable across three groups) followed by sensitivity analyses using BOCF, BOCF/LOCF hybrid and MMRM. These sensitivity test methods were recommended by the Division (DAARP) and are generally acceptable to test sensitivity of a primary LOCF imputation for analgesic and OA trials. The secondary analyses included ANCOVA using PP/LOCF and the comparison of effect size between PN400 and celecoxib.

Primary endpoints:

- Both PN400 and celecoxib were statistically superior to placebo in primary and sensitivity analyses (BOCF, BOCF/LOCF hybrid and MMRM) of three co-primary endpoints.
- However, in contrast to the ITT/LOCF primary analysis, the PP/LOCF analysis (a secondary analysis) failed to show superiority of both PN400 and celecoxib over placebo in WOMAC Pain and WOMAC Function. The Applicant’s explanation in the response to the DAARP’s request on Dec 18, 2009 appears reasonable:
 - Unexpectedly high placebo response, probably due to the informed consent indication an 80% possibility of receiving one of active treatments (2:2:1 randomization).
 - The unbalanced randomization (2:2:1) would favor placebo when there is missing data
 - The PP population was smaller than the ITT and thus had lower statistical power.
- PN400 had numerically larger effect size than celecoxib in all analyses (primary, secondary and sensitivity) of WOMAC Pain and Function and in sensitivity analyses of PGA. There was slightly smaller effect size with PN400 than celecoxib in the ITT/LOCF and PP/LOCF analyses.
- Non-inferiority between PN400 and celecoxib was established based on the sponsor’s pre-specified NI margin with primary analysis, secondary analyses and sensitivity analyses (ITT/without LOCF, BOCF, BOCF/LOCF Hybrid and MMRM).

Secondary endpoints, all secondary endpoints including WOMAC Index and PGA at Week 6, WOMAC Stiffness and Total at Week 12, WOMAC Pain and APS-POQ on Days 1-7, MDHAQ, and rescue analgesic use were supportive to the primary endpoints (non-inferiority to celecoxib and superiority to placebo).

GI tolerability was assessed as part of secondary objectives and secondary endpoints (mSODA, heartburn-free days, incidence of NSAID-associated GI events and rescue antacid use).

- PN400 showed numerically less GI benefit than celecoxib in mSODA at Weeks 6 and 12. Subgroup analysis of mSODA by aspirin use showed that PN400 was numerically better than celecoxib and placebo in the aspirin users but statistically worse than celecoxib in the non-aspirin users.
- For the other GI endpoints, PN400 appeared similar to or slightly better than celecoxib and placebo.

Safety:

There were no deaths reported during the study. A few subjects experienced serious AEs, which were mostly confounded by a history of medical conditions. No new safety signals associated with PN400 and celecoxib were identified from the study as compared with safety profiles presented in the latest labeling of naproxen (Naprosyn, Celebrex and Nexium). The GI disorders were the most common AEs with comparable frequency among PN400, celecoxib and placebo, which was likely confounded by the high background of GI events (prior NSAID use).

CONCLUSION AND DISCUSSION:

- PN400 is efficacious for treatment of signs and symptoms of osteoarthritis of the knee based on the superiority analysis (PN400 over placebo).
- The non-inferiority of PN400 over celecoxib can not be established based on totality of efficacy outcome and inadequate pre-specified NI margin. The upper bound of 95% CI of the effect size of celecoxib (vs. placebo) resulted from this trial was 11.98 mm for WOMAC Pain and 11.23 for WOMAC Function, which was less than 2 mm from the NI margin (10 mm). Because of intrinsic limitations of analgesic trials (such as high variations, small treatment size, and inconsistent outcome across studies), the non-inferiority of an analgesic with others is highly uncertain.
- The GI tolerability is inconclusive because the GI outcomes may have been confounded by the high background of NSAID-associated GI disorders (more than 93% subjects used NSAIDs prior to the study) and there was no naproxen alone as a comparator.
- No new safety signals were identified in the trial.

Study PN400-309

Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy of PN400 bid and Celecoxib 200 mg qd in Patients with Osteoarthritis of the Knee

Study location: US (80 sites)

Study report date: May 1, 2009

Study period: April 9 to Dec 30, 2008

STUDY DESIGN

This study was a replicated trial of the Study 307. The study design and conduct were identical to Study 307, including primary/secondary objective, overall study design (12-week, placebo-controlled, non-inferiority), subject selection (and number), treatment regimen, efficacy and safety assessments, and statistical analysis plan (analysis populations, non-inferiority margin, primary analysis, secondary analyses). The visit and assessment schedule are shown in Table 19.

Amendments to the protocol:

The trial appears to have been conducted as originally designed (by following the original protocol) except with the following protocol amendments:

Amendment #1: dated on Feb 18, 2008 (prior the study start) with the following protocol changes:

- clarified footnotes for the schedule of events table
- defined visit windows
- revised and refined inclusion criteria
- specified randomization criteria
- provided for upper and lower reference points for the pain scales on the APS-POQ sample questionnaire
- increased the number of sites
- changed the recall time for the heartburn question
- clarified rescue medication use and analysis

Amendment #2: dated on September 10, 2008 (near the end of the study) with the following protocol changes:

- changed the primary analysis population to the ITT
- clarified the statistical analysis, rescue medication sections
- changed the population of the primary analysis from the PP to include the ITT (as per DAARP's comments in the June-24-2008 meeting minutes)

Table 19. Visit and Assessment Schedules
(From sponsor's Table 2 in the Study 309 report)

Weeks	Screening	OA Flare Determination	Baseline/ Randomization	Treatment			
	-1(-2)	7-14 Days after Screen	0	1 +/- 2 Days	6 +/- 3 Days	12 +/- 3 Days	
Visit	1		2	Day 1-6	3 Day 7	4	5
Informed consent	X						
In/exclusion criteria	X						
ECG	X						
Medical history	X		X				
Laboratory tests	X		X ¹	X	X	X	X
Vital signs	X		X	X	X	X	X
Physical examination	X						X
Urine Pregnancy test ²	X		X	X	X	X	X
Dispense acetaminophen	X		X			X	
Randomization			X				
Dispense study drug			X			X	
Dispense/return e-diary			X				X
Dispense antacids			X			X	
Study drug and rescue med accountability						X	X
Prior and concomitant medications	X		X		X	X	X
Adverse events ³			X		X	X	X
WOMAC ^{4,5,6}	X ⁵	X ⁵	X ⁹	X ⁶	X ⁶	X	X
Heartburn assessment ^{4,7}			X	X	X	X	X
PGA (5-point Likert scale) ⁴	X	X	X ⁹	X	X		
PGA (VAS) ⁴			X		X	X	X
APS-POQ ⁴			X	X	X		
mSODA ^{4,7}			X	X	X	X	X
MDHAQ			X		X	X	X
OMERACT-OARSI OA Responder Index						X	X
Subject study drug adherence ⁷				X	X	X	X
Subject rescue medication use ⁸				X	X	X	X

1 = Repeat laboratory tests at Baseline if > 14 days from Screening to Baseline

2 = Women of child-bearing potential

3 = Serious adverse events were captured from time of informed consent, non-serious adverse events from the time of first intake of study drug.

4 = Electronic efficacy assessments were completed in the morning prior to study drug dosing

5 = Question 1, WOMAC Pain Subscale (administered at Screening and at OA flare determination)

6 = WOMAC Pain Subscale only

7 = Completed daily using subject take-home e-diaries

8 = Completed as needed using subject take-home e-diaries

9 = PGA (Likert scale) and Question 1 of the WOMAC were transferred to the Baseline Visit in the e-diary once the subject had a qualifying OA flare.

RESULTS

Disposition of subjects

Total enrollment:

N= 615 subjects were enrolled from 82 study centers and randomized to the following three groups (Table 20). [Enrollment of a total of 570 patients from approximately 80 study sites was planned.]

- n=244 to PN400
- n=247 to celecoxib
- n=124 to placebo

Overall disposition of subjects was comparable across the three groups. Approximately 99% (n=610) received ≥ 1 dose of study medication (as the Safety Population).

Dropouts: overall dropout rate was 21% (n=126), with less dropouts in the PN400 group (17%) than in the celecoxib (23%) and placebo groups (21%), and the most common reasons for dropouts were AEs, followed by withdrew consent (Table 20). In the Applicant’s report, “Lack of Efficacy” were not stratified but included in “Withdrew Consent” and “Others”. However, as per the statistical reviewer (Ms. Katherine Meaker), the dropouts due to “Lack of Efficacy” were classified in the sensitivity analyses such as BOCF/LOCF.

Table 20. Disposition of subjects
(From the Applicant’s Table 4 in Study 309)

	PN 400 bid N=244	Celecoxib 200 qd N=247	Placebo N=124	Total N=615
	n (%)	n (%)	n (%)	n (%)
Treated (Safety Population)	243 (99.6)	245 (99.2)	122 (98.4)	610 (99.2)
Intent-to-Treat Population	241 (98.8)	244 (98.8)	122 (98.4)	607 (98.7)
Per-Protocol Population	224 (91.8)	214 (86.6)	109 (87.9)	547 (88.9)
Completed Study	203 (83.2)	188 (76.1)	98 (79.0)	489 (79.5)
Prematurely Discontinued	41 (16.8)	59 (23.9)	26 (21.0)	126 (20.5)
Adverse Event	16 (6.6)	22 (8.9)	6 (4.8) ¹	44 (7.2)
Withdrew Consent	17 (7.0)	25 (10.1)	15 (12.1)	57 (9.3)
Lost to Follow-up	3 (1.2)	3 (1.2)	1 (0.8)	7 (1.1)
Other	5 (2.0)	9 (3.6)	4 (3.2)	18 (2.9)

Source: Table 14.1.1

¹Includes 1 subject who did not treat with study drug.

Based on recalculation of reasons for dropouts using the Applicant’s dataset ADSL, the common reasons for dropout were AEs in the active treatment groups and “withdrew consent” in the placebo group, followed by lack of efficacy (Table 21). Three dropouts in the celecoxib group were mis-categorized from AEs to “withdrew consent” in the Applicant’s report, which may not impact the analysis outcome (because celecoxib failed to show superiority to placebo).

Table 21. Reasons for dropouts in Study 309
(Calculated from the Applicant’s dataset ADSL – Subject Level Analysis Dataset)

Reason for Dropout	PN400 (500/20mg bid)	Celecoxib (200 mg qd)	Placebo	Total
	N=244	N=247	N=124	N=615
	n (%)	n (%)	n (%)	n (%)
Total	41 (16.8)	59 (23.9)	26 (21.0)	126 (20.5)
Adverse Event	16 (6.6)	25 (10.1)	6 (4.8)	47 (7.6)
Lack of efficacy	7 (2.9)	11 (4.5)	6 (4.8)	24 (3.9)
Withdrew Consent	10 (4.1)	12 (4.9)	15 (12.1)	37 (6.0)
Lost to Follow-up	3 (1.2)	3 (1.2)	1 (0.8)	7 (1.1)
Other	5 (2.0)	8 (3.2)	2 (1.6)	15 (2.4)

Protocol violation

A total of 68 subjects with major protocol violation and were excluded from the PP population. The violations are listed in Table 22.

- N=20 subjects (8%) from the PN400 group
- N=33 subjects (13%) from the celecoxib group
- N=15 subjects (12%) from the placebo group

Table 22. Major protocol violation and exclusion from the PP population
(From the Applicant’s Table 5 of Study 309 report)

	PN 400 bid N=244	Celecoxib 200 qd N=247	Placebo N=124
	n	n	n
Noncompliance	14	25	12
Disallowed Medication Used	3	2	1
Did Not Take Any Study Medication	1	2	2
No Post-baseline Efficacy Evaluations	2	1	0
OA Flare Criteria Not Met	0	2	0
Inclusion/exclusion criteria not met	0	1	0

Source: [Table 14.1.3](#)

Note: Subjects could have been excluded for more than 1 reason, but only 1 is listed. Non-compliance takes priority. For complete reference see [Table 14.1.3](#)

Demographics

Demographics in the ITT population were generally comparable across the three groups: mean age of 62 years (50-89) with 64% females, except slightly fewer subjects in the placebo group were smokers (9% vs. 14.5% in PN400 and 16.8% in celecoxib).

Baseline characteristics

Baseline characteristics in the ITT population and PP population were generally comparable across three groups,

- Past and current medical conditions: All subjects had current co-morbid conditions. The most common conditions were in musculoskeletal and cardiovascular systems. GI disorders were 39% (current) and 20% (past), which was comparable across groups.
- OA medications: NSAIDs were most commonly used, in $\geq 95\%$ of subjects (37% on ibuprofen, 28% on naproxen, 15% on celecoxib and 15% on others including meloxicam, diclofenac, nabumetone, etodolac) (Table 23). Overall, the use of OA medications was balanced across groups except use of celecoxib (see the following).

The following baseline characteristics were slightly unbalanced:

- Severity of OA in the PN400 group was slightly lower (fewer subjects with ACR Functional Class III): 19% in PN400 group, 30% in celecoxib and 25% in placebo.
- About 23% subjects took low-dose-aspirin (LDA) with fewer LDA users in the celecoxib group: 18% vs. 28% in the PN400 and 23% in the placebo.
- About twice as many subjects in the celecoxib group used celecoxib before the study.

Table 23. Previous use of analgesics
(From the Applicant's Table 14.1.9.1 of Study 309)

Analgesics	PN400 (N=241)	Celecoxib (N=244)	Placebo (N=122)	Total (N=607)
	n (%)	n (%)	n (%)	n (%)
Ibuprofen	94 (39%)	81 (33%)	47 (39%)	222 (37%)
Naproxen	65 (27%)	70 (29%)	37 (30%)	172 (28%)
APAP	55 (23%)	54 (22%)	36 (30%)	145 (24%)
Celecoxib	28 (12%)	50 (21%)	12 (10%)	90 (15%)
Opioids (combo)	10 (4.1%)	7 (2.9%)	3 (2.5%)	20 (3.3%)

ITT Population for primary analysis:

The primary efficacy analysis, as per the Applicant's SAP, was based on ITT population with LOCF imputation. The subjects included in the Applicant's ITT/LOCF analysis are shown in Table 24.

Table 24. ITT Population for primary analysis (LOCF imputation)
(From the Applicant’s untitled summary table in Page 55 of the Study 309 report)

	PN 400	Celecoxib	Placebo
Total ITT	241	244	122
WOMAC Pain and Function			
Subjects with no post-baseline value ¹	28 (12%)	24 (10%)	16 (13%)
Subjects included in LOCF Analysis	213 (88%)	220 (90%)	106 (87%)
Subjects with Week 12 value	175 (73 %)	161 (66 %)	89 (73 %)
Subjects with Week 6 value only ²	38 (16 %)	59 (24 %)	17 (14 %)
PGA-VAS			
Subjects with no post-baseline value ¹	6 (2%)	10 (4%)	7 (6%)
Subjects included in LOCF Analysis	235 (98%)	234 (96%)	115 (94%)
Subjects with Week 12 value	179 (74 %)	165 (68 %)	91 (75 %)
Subjects with Week 6 value only ²	56 (23 %)	69 (28 %)	24 (20 %)

Source: [Table 14.2.5.1](#)

¹ Excluded from Last Observation Carried Forward (LOCF) analysis

² Week 6 value carried forward to impute missing Week 12 value

Primary analysis of primary endpoints

The Applicant’s primary ITT/LOCF analysis of three co-primary endpoints showed that PN400 was non-inferior to celecoxib, and PN400, but not celecoxib, was superior to placebo (Table 25):

- PN400 met the pre-specified NI margin compared to celecoxib in three co-primary endpoints:
 - The upper bound of the 95% CI was ≤ 10 mm for WOMAC Pain (3.34 mm) and WOMAC Function (2.6 mm).
 - The lower bound of the 95% CI was ≥ -10 mm for the PGA-VAS (-1.41).
- PN400, *but not celecoxib*, was statistically superior to placebo in all three co-primary endpoints with the numerically larger treatment sizes than celecoxib.

Table 25. Primary Analysis of Non-inferiority (vs. Celecoxib) and Superiority (vs. Placebo) in ITT population with LOCF imputation

(From the Applicant's Tables 8, 9, 10 and 12 of Study 309 report)

Three Co-primary Endpoints*	PN400 N=241	Celecoxib N=244	Placebo N=122	PN400 <i>minus</i> Celecoxib	Differences from Placebo	
					PN400	Celecoxib
WOMAC Pain						
n	213	220	106			
Baseline Mean (SD)	69.6 (18.2)	71.3 (16.6)	67.9 (18.8)			
LS Mean	-44.24	-42.94	-38.38	-1.30	-5.81	-4.56
95% CI				(-5.94, 3.34)	(-11.60, -0.12)	(-10.28, 1.16)
p-value					P=0.045	P=0.118
WOMAC Function						
n	213	220	106			
Baseline Mean (SD)	66.7 (20.3)	68.7 (18.5)	64.6 (21.8)			
LS Mean	-38.90	-36.79	-32.32	-2.11	-6.59	-4.47
95% CI				(-6.82, 2.60)	(-12.41, -0.76)	(-10.28, 1.33)
p-value					P=0.027	P=0.131
PGA-VAS						
n	235	234	115			
Baseline Mean (SD)	32.2 (23.4)	29.6 (20.4)	29.5 (18.5)			
LS Mean	29.03	25.58	21.39	3.45	7.64	4.18
95% CI				(-1.41, 8.31)	(1.65, 13.63)	(-1.80, 10.17)
p-value					P=0.013	P=0.170

* Least Square (LS) Mean changes from baseline at Week 12 and the 95% CI were calculated with ANCOVA (Analysis of Covariance) using baseline as a continuous covariate. A negative change in the WOMAC Pain and Function and a positive change in the PGA-VAS indicate improvement.

Secondary analyses of primary endpoints:

There were two secondary analyses for the primary endpoints as planned in the protocol: PP/LOCF analysis and comparison of effect size.

PP/LOCF analysis (Table 26):

- PN400 was non-inferior to celecoxib for the three co-primary endpoints. The LS mean differences in the three co-primary endpoints between PN400 and celecoxib were numerically smaller with the PP analysis than with the ITT analysis (less favorable to PN400, suggesting the PP/LOCF analysis was less sensitive than the ITT/LOCF).
- Like results from the ITT/LOCF analysis, PN400, *but not celecoxib*, was statistically superior to placebo in all three co-primary endpoints.

Comparison of effect size:

With either ITT/LOCF analysis (Table 25) or PP/LOCF analysis (Table 26), PN400 had larger effect sizes than celecoxib. However, this does not support the non-inferiority of PN400 over celecoxib because celecoxib was not statistically superior to placebo in both analyses.

Table 26. Non-inferiority and superiority Analyses in PP population with LOCF imputation
(From the Applicant’s Table 11 and Table 14.2.5.2 of Study 309 Report)

Three Co-primary Endpoints	PN400 N=224	Celecoxib N=214	Placebo N=109	PN400 <i>minus</i> Celecoxib	Differences from placebo	
					PN400	Celecoxib
WOMAC Pain						
n	203	199	102			
LS Mean	-44.75	-43.77	-38.67	-0.98	-6.09	-5.11
95% CI				(-5.70, 3.74)	(-11.83, -0.34)	(-10.88, 0.66)
p-value					P=0.038	P=0.083
WOMAC Function						
n	203	199	102			
LS Mean	-39.30	-37.67	-32.62	-1.63	-6.68	-5.05
95% CI				(-6.46, 3.19)	(-12.55, -0.82)	(-10.95, 0.85)
p-value					P=0.026	P=0.093
PGA-VAS						
n	222	208	107			
LS Mean	29.34	26.58	20.62	2.76	8.72	5.96
95% CI				(-2.28, 7.80)	(2.58, 14.87)	(-0.24, 12.16)
p-value					P=0.006	P=0.0596

Sensitivity analyses of primary endpoints

There were four sensitivity analyses to test the primary ITT/LOCF analysis:

- **Pre-specified sensitivity analysis** – non-inferiority analysis using ITT population/without LOCF imputation (pre-specified in SAP) showed a similar NI results (Table 27) to the primary analysis.

Table 27. Sensitivity analysis of non-inferiority in ITT/without LOCF
(From the Applicant’s Table 14.2.3 in Study 309)

Three Co-primary Endpoints*	PN400 N=241	Celecoxib N=244	PN400 minus Celecoxib
WOMAC Pain: n	175	161	
LS Mean	-45.51	-46.00	0.49
95% CI			(-4.52, 5.50)
WOMAC Function: n	175	161	
LS Mean	-40.52	-39.73	-0.78
95% CI			(-5.98, 4.41)
PGA-VAS: n	179	165	
LS Mean	30.80	29.46	1.33
95% CI			(-4.24, 6.91)

* LS Mean changes from baseline at Week12.

- **Post-hoc sensitivity analyses:** The three post-hoc sensitivity analyses (BOCF, LOCF/BOCF hybrid and MMRM, as defined in the above Study 307 review) were submitted in ISE (Section 2.2.5, p77-78):
 - Differences (about 4 mm) between PN400 and celecoxib were within the pre-specified NI margin for all three co-primary endpoints (Table 28)
 - PN400 was statistically superior to placebo with hybrid BOCF/LOCF and MMRM but failed with BOCF for all three co-primary endpoints (Table 29).
 - Like results from primary LOCF analysis, celecoxib was not statistically different from placebo in all three co-primary endpoints using three sensitivity analyses (Table 29).

Table 28. Post-hoc sensitivity testing of primary non-inferiority analysis
(From the Applicant’s Table 5.3.5.3.1.25 in ISE, p78, for Study 309)

	WOMAC Pain (95% CI)	WOMAC Function (95% CI)	PGA-VAS (95% CI)
LOCF per SAP Sensitivity Analysis	-1.30 (-5.94, 3.34)	-2.11 (-6.82, 2.60)	3.45 (-1.41, 8.31)
BOCF	-2.10 (-7.28, 3.07)	-2.22 (-7.17, 2.73)	2.15 (-2.69, 7.00)
Hybrid BOCF- LOCF	-1.91 (-6.93, 3.10)	-2.43 (-7.31, 2.45)	4.16 (-0.71, 9.02)
MMRM	-1.38 (-3.95, 1.19)	-1.49 (-4.10, 1.13)	1.52 (-1.17, 4.20)

Source: PN400-309 Table 14.2.1, Table E2.30, Table E2.31, Table E2.32

Data represented the differences in the LS Mean change from baseline at Week 12 between PN400 and celecoxib, and 95% CI of the difference.

Table 29. Post-hoc sensitivity testing of primary superiority analysis
(From the Applicant’s Table 5.35.3.1.27 in ISE, p80, for Study 309)

	WOMAC Pain		WOMAC Function		PGA-VAS	
	Diff.	p-value	Diff.	p-value	Diff.	p-value
LOCF per SAP						
PN 400 - Placebo	-5.86	0.0453	-6.59	0.0267	7.64	0.0125
Celecoxib - Placebo	-4.56	0.1179	-4.47	0.1305	4.18	0.1702
Sensitivity Analysis						
BOCF						
PN 400 - Placebo	-3.02	0.3485	-3.60	0.2433	3.12	0.3010
Celecoxib - Placebo	-0.92	0.7752	-1.38	0.6544	0.97	0.7478
Hybrid BOCF- LOCF						
PN 400 - Placebo	-6.17	0.0483	-6.54	0.0317	6.54	0.0311
Celecoxib - Placebo	-4.26	0.1721	-4.11	0.1764	2.38	0.4307
MMRM						
PN 400 - Placebo	-4.61	0.0040	-4.60	0.0047	3.86	0.0204
Celecoxib - Placebo	-3.23	0.0432	-3.12	0.0557	2.35	0.1597

Source: PN400-309 Table 14.2.5.1, Table E2.33, Table E2.34, Table E2.35

Data represented the differences in the LS Mean change from baseline at Week 12 between active and placebo.

Verifications by the statistical reviewer (Ms. Katherine Meaker): The Applicant’s analyses were verifiable. However, the non-inferiority of PN400 over celecoxib can not be established because celecoxib was not superior to placebo in all three co-primary endpoints and the pre-specified NI margin was inadequate. The re-analyses using the adjusted NI margin computed from the effect size between celecoxib and placebo show that PN400 is not non-inferior to celecoxib. See the statistical review for details.

Secondary endpoints

The Applicant’s pre-specified secondary endpoints and their analyses are regrouped as follows:

WOMAC Index and PGA at Week 6

The LS mean changes from baseline at Week 6 in WOMAC Index (Pain, Function and Stiffness), WOMAC Total and PGA according to the Applicant’s ITT/LOCF analysis showed that PN400 had numerically more improvement than celecoxib and PN400, but not celecoxib, was statistically superior to placebo (Table 30).

WOMAC Stiffness and Total at Weeks 12

The LS mean changes from baseline at Week 12 according to the Applicant’s ITT/LOCF analysis showed a similar outcome as at Week 6.

- WOMAC Stiffness:
 - PN400 had numerically more improvement than celecoxib (-39.91 vs. -35.91).
 - PN400, but not celecoxib, was statistically superior to placebo (effect size: -6.71 vs. -2.70).

- WOMAC Total score:
 - PN400 had numerically more improvement than celecoxib (-41.49 vs. -39.77).
 - PN400, but not celecoxib, was statistically superior to placebo (effect size: -6.46 vs. -4.74).

Table 30. Secondary endpoints: WOMAC Index and PGA at Week 6
(From Applicant’s Table 14.2.9 and Table 14.2.10 in Study 309)

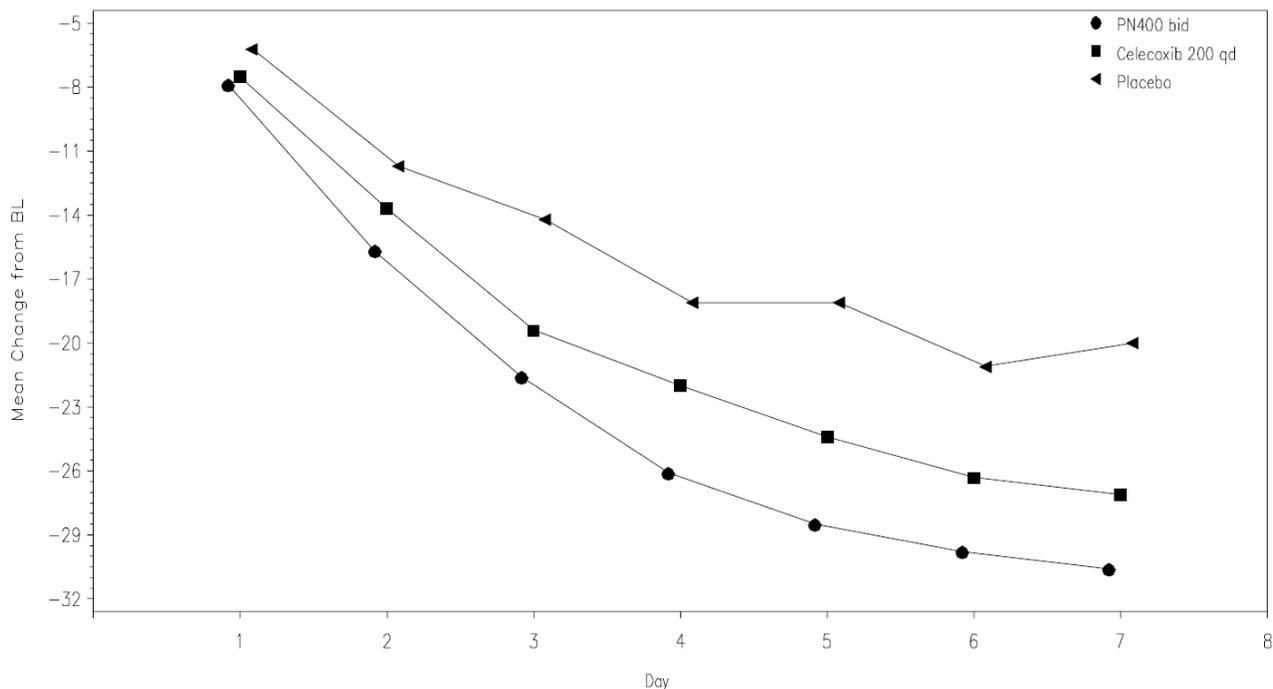
Secondary Endpoints*	PN400 N=241	Celecoxib N=244	Placebo N=122	PN400 minus Celecoxib	Differences from Placebo	
					PN400	Celecoxib
WOMAC Pain						
n	188	197	96			
LS Mean	-44.27	-39.09	-35.06	-5.18	-9.21	-4.03
95% CI				(-10.06, -0.30)	(-15.23, -3.20)	(-10.01, 1.94)
WOMAC Function						
n	188	197	96			
LS Mean	-38.52	-33.83	-30.52	-4.69	-8.00	-3.31
95% CI				(-9.56, 0.18)	(-13.99, -2.00)	(-9.27, 2.65)
WOMAC Stiffness						
n	188	197	96			
LS Mean	-39.91	-35.91	-33.20	-4.01	-6.71	-2.70
95% CI				(-9.19, 1.17)	(-13.09, -0.33)	(-9.03, 3.63)
WOMAC Total						
n	188	197	96			
LS Mean	-40.91	-36.30	-32.85	-4.61	-8.07	-3.45
95% CI				(-9.41, 0.19)	(-13.98, -2.15)	(-9.33, 2.42)
PGA-VAS						
n	233	233	114			
LS Mean	27.38	23.56	21.04	3.82	6.34	2.51
95% CI				(-0.87, 8.52)	(0.55, 12.12)	(-3.27, 8.29)

WOMAC Pain on Days 1-7

The LS mean changes from baseline in WOMAC Pain (*average daily pain scores*) on Days 1-7 according to the Applicant’s ITT/LOCF analysis are shown in Figure 7:

- PN400 had more pain improvement than celecoxib at all time-points from day 2 to day 7.
- The differences from placebo were statistically significant from Days 3-7 for PN400 and on Days 3, 5 and 7 for celecoxib.

Figure 7. Time-course of LS Mean change in WOMAC Pain from baseline at Days 1-7
(From Applicant's Figure 14.2.13.2 in Study 309)



APS-POQ on Days 1-7

The American Pain Society – Patient Outcome Questionnaire (APS-POQ) questionnaire was administered daily for the first 7 days (Days 1-7).

- Questions 1-4 (pain *now*, *worst* and *average pain in the last 24 hours*)
 - PN400 was similar to celecoxib from day 1, with numerically better than celecoxib on most days.
 - Both active treatments were superior to placebo on most days after day 2 with more days for PN400.
- Question 5 (pain *interfered with activities*): overall on each day after Day 1
 - PN400 was numerically better than celecoxib on most days, differences on some days were statistically significant.
 - Both active treatments were superior to placebo in most activities on most days after Day 3. The effect sizes for PN400 were larger than those for celecoxib.

MDHAQ

LS mean changes from baseline at weeks 6 and 12 in the *Multi-dimensional Health Assessment Questionnaire* (MDHAQ) Physical Function, Pain and Global Health Status scores and overall scores (RAPID-3: Rheumatology Assessment of Patient Index Data) according to the Applicant's ITT/LOCF analysis (see Applicant's Table 14.2.11):

- PN400 was numerically better than celecoxib.
- PN400, but not celecoxib, was superior to placebo in RAPID-3 (and most individual categories) at Weeks 6 and 12.
- Improvement in physical function at Week 6 and Week 12 was not significantly different in any of the pair-wise comparisons.

- The overall improvement at Week 12 was similar or slightly greater than at week 6.

Time to First Response in PGA

Daily response (“good” or “excellent”) on PGA-Likert scale during Days 1-7 was assessed:

- The median time to response was 6.0 days with PN400 and 7.0 days with celecoxib and placebo (not statistically different).
- Responder rate was approximately 51% with PN400, 47% with celecoxib and 48% with placebo.

Rescue Acetaminophen

- Time to first rescue: the median time to first acetaminophen was comparable across three groups, with slightly earlier to take antacid in placebo groups.
- Percent of days for rescue: PN400 had slightly less % days than celecoxib and placebo (% rescue days: PN400<celecoxib<placebo).
- Rescue tablets taken per month: fewer tablets of acetaminophen were used by subjects in the PN400 group compared to celecoxib and placebo (tablets/month: PN400<celecoxib<placebo). The difference between PN400, but not celecoxib, and placebo was statistically significant.

OMERACT-OARSI

Outcomes Measures in Arthritis Clinical Trials – Osteoarthritis Research Society International (OMERACT-OARSI) was proposed as an exploratory analysis. The percent of subjects who met the OMERACT-OARSI criteria was greater with PN400 than celecoxib and placebo at both Week 6 (76%, 70% and 60%) and Week 12 (76%, 75% and 65%). The differences between PN400 and placebo at Week 6 and Week 12, and between celecoxib and placebo at Week 12 were statistically significant.

Concomitant Medications

Approximately 87% of subjects took other medications, mostly lipid modifying agents followed by anti-platelet agents and multivitamin. Less than 2% subjects used other analgesics or GI agents. Overall distribution of the concomitant medications was comparable across three groups.

GI tolerability

The GI tolerability was evaluated with *mSODA*, *heartburn-free days*, *pre-specified NSAID-associated events*, *rescues antacid use* and *treatment-emergent GI events* during the study. Overall, subjects treated with PN400 had similar or slightly better GI tolerability compared to celecoxib and placebo (Table 31).

More than 95% of subjects took NSAIDs (mostly ibuprofen, naproxen or celecoxib) prior to the study, which was comparable across three groups, see the above Baseline Characteristic for details). Therefore, a high event rate of NSAID-associated GI disorders should be expected at baseline in the study population. However, the detailed baseline GI event rates across three groups were reported in the study.

Table 31. GI tolerability Assessment

(From the Applicant's Tables 13, 15, 20, 14.3.3.1 and 14.2.16.2 in Study 309)

GI tolerability measures	PN400 N=241	Celecoxib N=244	Placebo N=122
mSODA (LS Mean)*	-4.03	-3.39	-4.29
Heartburn-free days (LS Mean)	74%	66%	66%
Pre-specified NSAID- associated events (incidence)	18.9%	21.6%	20.5%
Rescue antacid use (% subjects)	49.8%	52.9%	53.3%
Treatment-emergent GI events (% safety population)#	25.1%	24.9%	26.2%

* LS Mean Change in the modified severity of dyspepsia assessment (mSODA) from baseline at Week 12.

The incidence was calculated based on the Safety Population.

Modified SODA (mSODA)

The LS Mean changes from baseline at Weeks 6 and 12 in the mSODA (Modified Severity of Dyspepsia Assessment) *average daily pain* score were similar across three groups. At Week 12 with LS Mean analysis, PN400 and celecoxib showed slightly less improvement of dyspepsia than in placebo; the difference between PN400 and celecoxib (-0.64) was not statistically significant (Table 32).

Table 32. mSODA Avery Daily Pain Sore in ITT population with LOCF

(From the Applicant's Tables 13 and 14 in Study 309)

Time Point	PN400 N=238	Celecoxib N=241	Placebo N=120	PN400 minus Celecoxib
Baseline				
Mean (SD)	12.4 (11.5)	11.6 (10.8)	10.5 (10.5)	
Week 6 Change from Baseline				
Mean (SD)	-4.0 (9.8)	-3.0 (8.7)	-3.2 (9.8)	
Week 12 Change from Baseline				
LS Mean	-4.03	-3.39	-4.29	-0.64
95% CI				(-1.84, 0.56) p=0.298

mSODA: Modified Severity of Dyspepsia Assessment.

The data were mean changes from baseline at Weeks 6 and 12, LS Mean for Week 12 but not Baseline and Week 6. The higher the negative value (change from baseline) means the less the severity of dyspepsia. Data for the differences between PN400 and celecoxib at Week 6 were not reported in Study 309.

Subgroup analysis of mSODA by low-dose aspirin use showed that PN40 was numerically better than celecoxib and placebo in the aspirin users (23% subjects in total) and no different from celecoxib but numerically worse than placebo in the non-aspirin users (Table 33).

Table 33. Subgroup analysis of mSODA by low-dose aspirin use in ITT/LOCF
(From Applicant's Table 14.2.7.1 in Study 309)

Aspirin use	PN400 N=245	Celecoxib N=237	Placebo N=123
<i>Aspirin users</i>			
n	67	43	27
LS mean	-4.83 [†]	-2.81	-2.82
<i>Non-Aspirin users</i>			
n	171	198	93
LS mean	-3.75 [‡]	-3.52	-4.65

Least square mean change in mSODA average daily pain scores from baseline at Week 12. [†]p=0.112 and [‡]p=0.745 between PN400 and celecoxib by ANCOVA; no statistical analyses available for the differences between active treatments and placebo.

Heartburn Resolution

The percent of days with no heartburn (LS Mean from baseline to Week 12) was greater in subjects treated with PN400 (74.0%) than with celecoxib (66.0%) and placebo (66.3%). The differences between PN400 and celecoxib or placebo were statistically significant. The similar trends at Week 6 were reported. However, data on the percent of subjects experienced heartburn during the study were not reported in the study.

NSAID-associated UGI AEs

The percent of subjects experiencing the pre-specified NSAID-associated UGI adverse events (including duodenal ulcers) was similar across three groups:

- PN400: n=46 (18.9%)
- Celecoxib: n=53 (21.6%)
- Placebo: n=25 (20.5%)

However, the incidences of the pre-specified GI event at the baseline were not reported.

Dropouts due to pre-specified NSAID-associated UGI AEs was 2%, with slightly lower rate in the PN400 group:

- PN400: 1%
- Celecoxib: 4%
- Placebo: 3%

Rescue antacid use:

- Time to first rescue: the median time to first antacid was comparable across three groups, with slightly earlier to take antacid in placebo groups.
- Percent of days for rescue: PN400 had slightly less % days than celecoxib and placebo (% days: PN400<celecoxib<placebo).

- Rescue tablets taken per month: fewer tablets of antacid were used by subjects in the PN400 group compared to celecoxib and placebo (tablets/month: PN400<celecoxib<placebo). The difference between PN400, but not celecoxib, and placebo was statistically significant.

Safety evaluation

Extent of exposure

- The overall exposure to the study medications was similar across three groups.
- The mean duration of exposure in the safety population (n=610 received \geq one dose) was 75 \pm 24 days and approximately 86% of subjects were dosed for > 6 weeks. The exposure duration was comparable across three groups
 - PN400 (n=243): 77 \pm 22 days
 - Celecoxib (n=245): 74 \pm 26 days
 - Placebo (n=122): 74 \pm 25 days
- The mean number of tablets and capsules taken per subject was larger with PN400 than celecoxib or placebo due to slightly low dropout rate and slightly more days on treatment.
- The mean number of tablets and capsules per month was lowest in the placebo group and highest in the celecoxib group.

Serious AEs:

No deaths in the study. Seven subjects experienced other SAEs (Table 34). No SAE occurred in more than 1 subject. There were no GI SAEs. The causality of those SAEs related to the study medication can not be determined (although the investigators concluded “unrelated to study medication”).

- PN400: n=3 (1%):
 - Hip fracture: A 67-yo female (Subject 8327) was hospitalized due to fall and right hip fracture five days post-randomization (7 tablets of PN400). The patient was discharged after routine management and discontinued from the study due to the event.
 - Chest pain: A 78-yo male (Subject 8375) was hospitalized due to experiencing chest pain five days post-randomization (unknown number of tablets of PN400 as per the sponsor) and discontinued from the study. The patient has history of diabetes, hypertension and hyperlipidemia. The follow-up was unsuccessful after the dropout.
 - Coronary artery disease: A 71-yo male (Subject 8302) was hospitalized due to atrial flutter after 71 days of PN400 (166 tablets) and later angiography confirmed stenosis of both left and right coronary arteries followed by a successful angioplasty procedure. The patient appeared no history of cardiovascular disease and CVD risk factors. The patient continued the study medication after the diagnosis. This event was *possibly related* to the study medication.
- Celecoxib: n=3 (1%):
 - Coronary artery disease: A 66-yo male (Subject 8186) was diagnosed coronary artery disease 14 days after completing the study. The patient had history of diabetes and was on the study medication for 84 days (131 capsules of celecoxib). He had a successful CABG procedure.
 - Allergic drug reaction: A 68-yo male (Subject 8350) was hospitalized due to allergic reaction occurred 58 days post-randomization (102 capsules of celecoxib) and

- discontinued from the study. The patient has history of allergic reactions to certain antibiotics and food and received antibiotics (Bactrim) for injury associated with biking accident prior to the ER visit.
- Back pain (radiculopathy): A 61-yo female (Subject 8459) was hospitalized due to back pain 69 days post-randomization (134 capsules of celecoxib). The patients had history of chronic back pain with lumbar spinal and cervical surgeries.
 - Placebo: n=1 (1%)
 - Stroke (subarachnoid hemorrhage): A 57-yo female (Subject 8092) was hospitalized due to stroke 5 days after completing the study (84-day study medication). The patient had cardiovascular history or risk factors. After stabilized, she was transferred to a rehabilitation facility.

Table 34. SAEs in Safety Population
(Summarized from the Applicant narratives in the Study 309)

SAE (PT)	PN400 N=243	Celecoxib N=245	Placebo N=122
Total	3 (1%)	3 (1%)	1 (1%)
Coronary artery disease	1	1	
Chest pain	1		
Hip fracture	1		
Allergic reaction		1	
Back pain (radiculopathy)		1	
Stroke			1

AE-related dropouts

The overall dropout rate due to AEs was 6.6% in the PN400 group, 9.0% in the celecoxib group and 4.1% in the placebo group. The most common SOC for the dropouts was GI Disorders with slightly lower GI-related dropouts in the PN400 group (1.6% vs. 3.7% in celecoxib and 2.5% in placebo). The most common GI disorders leading to dropout were upper abdominal pain and gastroesophageal reflux disease.

Common AEs:

Approximately 50% of subjects experienced at least one treatment-emergent AE during the study, with slightly more AEs reported from active treatment groups than from placebo. Overall, there were no new safety signals compared to history of both NSAIDs.

The GI-related AEs were most common and were comparable across three groups:

- PN400: n=61 (25.1%)
- Celecoxib: n=61 (24.9%)
- Placebo: n=32 (26.2%)

Clinical laboratory:

Hematology and blood chemistry were tested at baseline and each visit. There were no clinically meaningful changes in the lab values, particularly those related to NSAID class, such as anemia, renal and liver functions.

Vital signs and physical exam:

The vital signs were monitored at all visits and physical exam were performed during screening and at the last visit (week 12). There were no clinically meaningful changes in vital signs and physical exams.

SUMMARY

Efficacy:

This was a replicated trial of Study 307: a 12-week, randomized, double-blind, placebo-/active-controlled, non-inferiority trial for the indication “treatment of signs and symptoms of OA”. The study subjects were patients with OA of the knee and were randomized at a ratio of 2:2:1 to PN400 bid (n= 241), celecoxib 200 mg qd (n=244) or placebo (n=122). Duration of the treatment was 12 weeks.

The standard three co-primary endpoints (mean change from baseline at week 12 in WOMAC Pain, WOMA Function and PGA) were used to establish non-inferiority of PN400 over celecoxib and superiority of the active treatments (PN400 and celecoxib over placebo). The NI margin was pre-specified as 10 mm difference (2-sided 95% CI) from celecoxib.

The primary analysis was ANCOVA in ITT population with LOCF imputation for dropouts (dropout rate of 16%, comparable across three groups) followed by sensitivity analyses using BOCF, BOCF/LOCF hybrid and MMRM. These sensitivity test methods were recommended by the Division (DAARP) and are generally acceptable to test sensitivity of primary LOCF imputation for analgesic and OA trials. The secondary analyses included ANCOVA using PP/LOCF and the comparison of effect size between PN400 and celecoxib.

Primary endpoints:

- PN400 was statistically superior to placebo in all three co-primary endpoints with primary, secondary and sensitivity analyses (BOCF/LOCF hybrid and MMRM but failed to BOCF).
- Celecoxib was numerically but not statistically superior to placebo in primary and secondary analyses and failed to all three sensitivity analyses.
- PN400 had numerically larger effect sizes than celecoxib for both primary and secondary endpoints and in all analyses of primary endpoints (primary, secondary and sensitivity analyses).
- Non-inferiority of PN400 over celecoxib was established according to pre-specified NI margin with all analyses (primary, secondary and sensitivity) of primary endpoints.

Secondary endpoints: all secondary endpoints (WOMAC Index and PAG at week 6, WOMNAC Pain on Days 1-7, APS-POQ, MDHAQ, etc.) were consistent with results from the primary endpoints and analyses.

GI tolerability was compared between PN400 and celecoxib based on evaluation of mSODA, heartburn-free days, pre-specified NSIAD-related GI events, and rescue use of antacid:

- For mSODA, PN400 was numerically better than celecoxib but worse than placebo. Subgroup analysis by aspirin use showed that in the aspirin users PN400 was numerically better than celecoxib and placebo but in the non-aspirin users PN400 was not different from celecoxib and numerically worse than placebo.
- Less antacid rescue use in PN400 group than in the celecoxib and placebo groups
- More heartburn-free days in PN400 than in celecoxib and placebo
- Slight lower NSAID-associated GI events with PN400 than with celecoxib and placebo.
- Celecoxib appeared similar to placebo in heartburn-free days but with slightly severer dyspepsia and slightly more in NSAID-associated GI events.

[Differences of Celecoxib groups from PN400 and placebo]

1. Slightly unbalanced baseline characteristics: in the celecoxib group
 - More subjects with severe OA conditions (ACR functional class III)
 - Fewer LDA users
 - More subjects with prior celecoxib use
2. Higher dropout rate in the celecoxib group: 24% (vs. 16% on PN400 and 21% on placebo)

Safety:

There were no deaths reported during the study. A few subjects experienced serious AEs, which were mostly confounded by history of medical conditions. No new safety signals associated with PN400 and celecoxib were identified from the study as compared with safety profiles presented in the latest labeling of naproxen (Naprosyn, Celebrex and Nexium). The GI disorder were the most common AEs with no differences among PN400, celecoxib and placebo, which was likely confounded by the high background of GI events (prior NSAID use).

CONCLUSION

- PN400 is efficacious for treatment of signs and symptoms of osteoarthritis of the knee based on the superiority analysis (PN400 vs. placebo).
- The non-inferiority of PN400 over celecoxib can not be established because celecoxib failed to superiority to placebo and the pre-specified NI margin was not adequate based on the effect size of celecoxib resulted from this study.
- The GI tolerability is inconclusive because the GI outcome may have confounded by the high background of NSAID-associated GI disorders (more than 95% subjects used NSAIDs prior to the study) and there was no naproxen alone as a comparator.
- No new safety signals were identified in the trial.

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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/

JIN CHEN
02/03/2010

ELLEN W FIELDS
02/03/2010
I concur with Dr. Chen's review

SHARON H HERTZ
02/03/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PN400-301 <p style="text-align: center;">Indication: Reducing the risk of Gastric Ulcers in patients at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers</p> Pivotal Study #2 PN400-302 <p style="text-align: center;">Indication: Reducing the risk of Gastric Ulcers in patients at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers</p>	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All studies conducted in the US.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		Table 14.1.8 135pt - 1 yr 491pts – 6 months 1326pts exposed during this clinical development However, both drugs components have been marketed for several years.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No deaths
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			(b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			The define.pdf file does not contain comments or possible values for any variables.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		Per sponsor additional forms available upon request

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

From DGPs, perspective there are no major review issues.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Erica Wynn, MD	August 18, 2009
Reviewing Medical Officer	Date
Ruyi He, MD	August 18, 2009
Clinical Team Leader	Date

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

/s/

ERICA L WYNN
08/20/2009

RUYI HE
08/20/2009