Clinical Study Report Synopsis

Drug Substance	PN 400
Study Code	D1120C00036
Edition Number	1
Date	13 September 2010

A Phase I Prospective, Randomized, Double-blind, Placebo-controlled Study Assessing Inhibition of Serum Thromboxane B2 Levels with PN 400 and Low-dose Aspirin

Study dates: First volunteer enrolled: 18 March 2010
Last subject last visit: 27 May 2010

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was conducted at a single center: Quintiles Phase I Services, Overland Park, Kansas, United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of this study was to determine if PN 400 coadministered with enteric-coated aspirin 81 mg (Day 11) was non-inferior at the 90% level to placebo coadministered with enteric-coated aspirin 81-mg, with respect to serum thromboxane B2 inhibition from baseline (Day 1).	Mean percent of inhibition of serum thromboxane B2, measured on the morning of Day 6 (Period 1), and 24 hours after the Day 10 morning dose of aspirin (ie, Day 11) in Period 2	Pharmacodynamic
Secondary	**Secondary**	
The secondary objective of this study was to evaluate safety and tolerability of PN 400 taken concurrently with low-dose aspirin.	adverse events, supine blood pressure and pulse rate, oral temperature, physical examination, and clinical laboratory variables	Safety

Study design

This was a single-center, randomized, double-blind, parallel group study in healthy male and female volunteers. A total of approximately 40 volunteers were enrolled in the study to ensure at least 32 evaluable volunteers.

Volunteers participated in 2 treatment periods. In Period 1 (Days 1 to 5), all volunteers received enteric-coated aspirin 81 mg once daily, at least 30 minutes prior to breakfast, for 5 days. In Period 2 (Days 6 to 10), volunteers were randomly assigned in a 1:1 ratio to receive 5 days of treatment with either enteric-coated aspirin 81 mg once daily plus PN 400 twice daily (Treatment A), or enteric-coated aspirin 81 mg once daily plus placebo twice daily (Treatment B), as follows:

- Treatment A: one tablet of PN 400 (naproxen 500 mg/esomeprazole 20 mg) plus 1 tablet of enteric-coated aspirin 81 mg administered at least 30 minutes prior to breakfast and 1 tablet of PN 400 (naproxen 500 mg/esomeprazole 20 mg) administered at least 30 minutes prior to dinner for 5 consecutive days; and

- Treatment B: One tablet of placebo (matched in appearance to PN 400) plus 1 tablet of enteric-coated aspirin 81 mg administered at least 30 minutes prior to breakfast

and 1 tablet of placebo (matched in appearance to PN 400) administered at least 30 minutes prior to dinner for 5 consecutive days.

All doses of study drug (aspirin, PN 400, and placebo) were administered under supervision of the Investigator/delegate. Volunteers were outpatient during Days 1 to 4, and inpatient on Days 5 to 11. Serum thromboxane B2 (TXB2) concentrations were measured predose on the mornings of Days 1 and 6, and at 24 hours after morning dosing on Day 10 (ie, on Day 11).

Target subject population and sample size

Healthy male and female volunteers within an age range of 50 to 75 years and a body mass index range of 19 to 30 kg/m^2, with no current or prior history of abnormal bleeding or bleeding disorders, clinically significant heartburn (as judged by the Investigator), ulcers, gastritis, or clinical laboratory test results indicative of abnormal coagulation were enrolled in this study.

Overall, 42 volunteers were enrolled in the study; 40 of these were randomly assigned to study treatment and included in the safety analyses.

The clinically relevant inhibition on TXB2 was defined as 90% of the inhibition achieved by treatment with aspirin alone. Under the assumption that for percent serum inhibition on TXB2 on Day 11, a one-sided 95% confidence interval of PN 400 would be at least 90%, with a standard deviation of 0.57%, and distance of 0.32% from mean to limit, 15 evaluable volunteers per group would yield 90% power to conclude non-inferiority above the 90% level. To account for potential dropouts, approximately 20 volunteers per group were assigned to randomization.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product: PN 400 tablets (naproxen 500 mg/esomeprazole 20 mg); administered orally twice daily on Days 6 to 10 with approximately 240 mL of water, at least 30 minutes before meals. Batch number: 3062846R

Comparator: Placebo (matching the investigational product in appearance, PN 400 tablets); administered orally twice daily on Days 6 to 10 with approximately 240 mL of water, at least 30 minutes before meals. Batch number: 3061523R

Additional study drug: Enteric-coated aspirin 81-mg tablets were administered once daily, with approximately 240 mL of water, at least 30 minutes before meals. It was administered alone on Days 1 to 5, and concurrently with PN 400 or placebo on Days 6 to 10, in the morning.

Duration of treatment

The study had 2 treatment periods of 5 days each, with no washout between periods. Along with a screening period of up to approximately 30 days and a follow-up period of

approximately 7 days, the total duration of the study for a volunteer was approximately 6 weeks.

Statistical methods

Serum thromboxane B2 concentrations and percent inhibition from baseline (Day 1) were listed and summarized by treatment and study day using descriptive statistics. Percent inhibition from baseline was defined as the difference in the serum TXB2 concentration on Day 1 minus that on Day 6 or on Day 11, divided by the Day 1 value, and expressed as a percentage, ie, [(baseline – postdose) / baseline]*100.

The primary hypothesis of this study was that concomitant multiple-dose administration of PN 400 does not interfere with the platelet inhibitory effects of enteric-coated low-dose aspirin (81 mg), as measured by serum TXB2 inhibition.

The primary statistical evaluation of treatment effect was based on the mean for serum TXB2 percent inhibition from baseline on Day 11 (ie, 24 hours following the Day 10 dose) for Treatment A (PN 400 plus aspirin). The mean percent inhibition from baseline values were calculated for each treatment with corresponding 90% confidence intervals, based on the t-distribution. The lower confidence limit of the two-sided 90% confidence interval (equivalent to the lower limit of a one-sided 95% confidence interval) for the mean percent inhibition for Treatment A and Treatment B (placebo plus aspirin) was subject to non-inferiority assessment separately. Non-inferiority was concluded if the lower confidence limit for Treatment A exceeded 90.0%, if assay sensitivity was established. Assay sensitivity was established if the lower confidence limit for Treatment B exceeded 90.0%.

Evaluable volunteers who were randomized, had no major protocol deviations during the study (including those affecting the integrity of the pharmacodynamic data), and whose serum thromboxane B2 percent inhibition was greater than or equal to 95% after 5 days of aspirin 81 mg (ie, Day 6 predose), were included in the primary pharmacodynamic assessment.

Safety data (adverse events, clinical laboratory evaluations, and vital signs) were summarized using descriptive statistics.

Subject population

There were a total of 42 study participants enrolled at a single study site in the United States; 40 of these volunteers were randomly assigned to either the PN 400 plus aspirin group (20 volunteers) or the placebo plus aspirin group (20 volunteers) and completed the study per protocol. The first subject was enrolled 18 March 2010 and the last subject last visit was 27 May 2010. The remaining 2 volunteers were withdrawn from the study during the aspirin only pretreatment phase prior to randomization. Demographics and baseline characteristics were comparable between the 2 treatment groups.

Eight of 40 (20%) completing volunteers (6 volunteers in the PN 400 plus aspirin group and 2 volunteers in the placebo plus aspirin group) were not evaluable for pharmacodynamics (ie, their serum TXB2 percent inhibition from baseline at Day 6 predose was less than 95%).

Summary of pharmacodynamic results

In the placebo plus aspirin group (pharmacodynamic population), the lower limit of the two-sided 90% confidence interval (equivalent to the lower limit of a one-sided 95% confidence interval) for percent inhibition from baseline on Day 11 was greater than 90% (actual value 98.7%), thus establishing assay sensitivity (at least 90% inhibition in the control group). The lower limit of the two-sided 90% confidence interval on Day 6 was 98.2%, and very similar to that observed on Day 11, thus demonstrating the consistency and reproducibility of these results.

In the PN 400 plus aspirin group, the lower limit of the two-sided 90% confidence interval (equivalent to lower limit of one-sided 95% confidence interval) on Day 11 was also greater than 90% (actual value 99.4%), thus demonstrating inhibition above the 90% threshold. Thus, with both treatments demonstrating inhibition above the 90% threshold, non-inferiority of PN 400 plus aspirin treatment with placebo plus aspirin treatment is concluded.

Summary of safety results

There were no deaths, serious adverse events, or discontinuations from the study due to adverse events. Overall, there were 18 treatment-emergent adverse events reported in 13 (32.5%) of the 40 volunteers randomly assigned to treatment group. The number of volunteers with treatment-emergent adverse events was higher for the placebo plus aspirin group (8/20 volunteers, 40%) versus the PN 400 plus aspirin group (3/20 volunteers, 15%) or during the aspirin pretreatment phase (3/40 volunteers, 7.5%).

The most frequently reported adverse events were excoriation, headache, and nasal congestion, occurring in 2 volunteers (5%) each. There was 1 adverse event of blood pressure increased; otherwise, there were no adverse events for clinical laboratory or vital sign findings.

One treatment-emergent adverse event of constipation was assessed as related to study drug (placebo plus aspirin); otherwise, all adverse events were considered not related. All reported adverse events were assessed as mild in intensity.

There were no trends or clinically relevant changes noted in clinical laboratory or vital sign data.