Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

2. SYNOPSIS

NAME OF SPONSOR/COMPANY Boehringer Ingelheim Pharmaceuticals, Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Aggrenox®		
NAME OF ACTIVE INGREDIENT Aggrenox®, dipyridamole 200 mg and acetylsalicylic acid 25 mg extended release capsule	Volume: Page:	

Title of Study: Drug-Drug Interaction Study of the Effect of Omeprazole 80 mg q.d. at Steady State on the Pharmacokinetics and Pharmacodynamics of Aggrenox® Every 12 Hours at Steady State in Healthy Male and Female Volunteers (an Open-Label, Randomized, Crossover Study)

Investigator(s): [redacted] MD

Study Center(s): [redacted]

Publication (Reference): Not applicable

Studied period:
(date of first enrollment)
15 March 2011

(**date of last completed**)
12 May 2011

PHASE OF DEVELOPMENT: I

Objectives: The objective of the current study was to investigate if a drug-drug interaction occurred with the administration of omeprazole 80 mg once daily (QD) at steady state on the pharmacokinetics (PK) of dipyridamole and the pharmacodynamics (PD) of acetylsalicylic acid (ASA)-induced platelet aggregation inhibition (components of Aggrenox®) when administered every 12 hours at steady state.

Methodology: Open-label, multiple-dose, randomized, crossover design with 4 treatments given in 2 sequences:

Treatment A: Aggrenox® twice daily for 7 days (every 12 hours)
Treatment B: Aggrenox® for 7 days (every 12 hours) and omeprazole daily for 7 days, following Treatment A
Treatment C: omeprazole 80 mg daily for 7 days
Treatment D: Aggrenox® twice daily for 7 days (every 12 hours) and omeprazole daily for 7 days, following Treatment C

Number of Subjects (Planned and Analyzed): A total of 60 subjects were enrolled in the study, and 51 subjects completed the study. There were 60 subjects included in the safety analyses and 57 in the PK and PD analyses.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

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Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test products were Aggrenox® (dipyridamole 200 mg and acetylsalicylic acid 25 mg [Aggrenox®] extended-release capsule), Batch number B103000523, in combination with omeprazole 40 mg (Prilosec®) delayed-release capsule (2 capsules administered to achieve an 80 mg dose), Batch number B103000524, taken orally with 240 mL of water.

Duration of Treatment: There were 2 treatment periods (Treatment A followed by Treatment B and Treatment C followed by Treatment D, in 2 treatment sequences: ABCD or CDAB) of approximately 14 days each with a washout phase of 14 days following Treatment B or Treatment D.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference product was Aggrenox® (dipyridamole 200 mg and acetylsalicylic acid 25 mg [Aggrenox®] extended-release capsule) administered alone, Batch number B103000523, taken orally with 240 mL of water.

Criteria for Evaluation:

Pharmacokinetics:

Primary Endpoints:
Systemic exposure to dipyridamole was primarily characterized by $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$.

Secondary Endpoints:
$C_{min,ss}$ and %PTF were secondary endpoints.

Pharmacodynamics:

Primary Endpoint:
Systemic exposure to ASA was characterized by the inhibition of platelet aggregation (IPA_4) at steady state and 4 hours after the last dose of Aggrenox®.

Secondary Endpoint:
Inhibition of platelet aggregation at steady state and 12 hours after the last dose of Aggrenox®.

Safety:

Physical examination, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead electrocardiogram (ECG), clinical laboratory tests (hematology, clinical chemistry, and urinalysis), and adverse events (AEs).

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Statistical Methods:

Pharmacokinetics:
Point estimators (geometric means) of the intra-subject ratios of $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$, as well as $C_{min,ss}$, and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical models were an analysis of variance (ANOVA) on log-transformed parameters with phenotype as a covariate.

A verification that dipyridamole steady-state concentrations had been reached was performed using a repeated measures ANOVA model on the logarithmic scale including 'time' as a repeated effect based on the predose samples on Days 5 - 7.

Descriptive statistics were calculated.

Pharmacodynamics:
The investigation of inhibition of platelet aggregation of acetylsalicylic acid at 4 and 12 hours were performed by an analysis of covariance (ANCOVA) on untransformed values for IPA with baseline and phenotype as covariates.

Descriptive statistics were calculated.

Pharmacogenomics: Dipyridamole PK parameters were summarized descriptively by phenotype. Phenotype was included in the PK ANOVA and PD ANCOVA primary analyses; they were found to be insignificant and were dropped from the models.

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SUMMARY – CONCLUSIONS

Demographic and Other Baseline Characteristics:

Of the 60 subjects participating in the study, 18 (30%) were female and 42 (70%) were male. Regarding race, 57 (95%) subjects were White, and 3 (5%) were Black or African American; with respect to ethnicity, 48 (80%) subjects were Hispanic or Latino, and 12 (20%) were not. The mean age for all subjects was 35.3 years (range 20 – 50 years), the mean weight was 75.69 kg (range 55.2 - 101.7 kg), and the mean body mass index (BMI) was 26.8 kg/m^2 (range 20.5 - 32.0 kg/m^2). A total of 51 subjects completed the study.

Pharmacokinetic Results:

Primary dipyridamole PK parameters $C_{max,ss}$ and $AUC_{0-12,ss}$, as well as secondary PK parameters ($T_{max,ss}$, CL/F, C_{avg}, $C_{min,ss}$, and %PTF) were similar between Treatments A, B, and D.

Treatment D versus Treatment A mean ratios for each primary dipyridamole PK parameter comparison were near 100% [92.03% for $C_{max,ss}$ and 96.38% for $AUC_{0-12,ss}$]. In addition, the 90% CIs fell within the accepted 80 - 125% bioequivalence target range. Results for the secondary comparisons of Treatment B versus Treatment A were similar with mean ratios of 92.30% for $C_{max,ss}$ and 97.03% for $AUC_{0-12,ss}$. $C_{min,ss}$, a secondary PK parameter, had a mean ratio of 106.09% and 90% CI within 80 - 125% for both the primary comparison, Treatment D versus Treatment A, as well as for the secondary comparison, Treatment B versus Treatment A. In addition, mean %PTF was similar for all treatments and ranged from 132 – 144%.

Pharmacodynamic Results:

IPA_4, the primary PD parameter, was similar between Treatments A, B, and D (range: 96.34 - 97.89%). IPA_{12}, a secondary PD parameter, was nearly identical to IPA_4, 97.80 - 98.78%. ASA almost completely inhibited platelet aggregation by 4 hours after dosing and the inhibition remained so at the end of the dosing interval at 12 hours postdose.

The primary statistical comparison, IPA_4 in Treatment D versus Treatment A, resulted in a mean ratio of 99.02% with a 90% CI of 98.32 – 99.72%. The secondary parameter, IPA_{12} in the comparison of Treatment D versus Treatment A, had a mean ratio of 99.38% with a 90% CI of 98.80 – 99.95%.

Results in the secondary statistical comparison, IPA_4 and IPA_{12} in Treatment B versus Treatment A, resulted in mean ratios of 98.42% and 99.02%, respectively, with 90% CIs of 97.66 - 99.18% and 98.46 – 99.59%, respectively.

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Safety Results:

There were no serious adverse events (SAEs) in this study. Two (2) subjects were discontinued by the Investigator during the Aggrenox® plus omeprazole arm due to AEs of moderate hypersensitivity and mild urticaria, both considered drug-related. A total of 53 (88%) subjects reported at least 1 treatment–emergent AE (TEAE) following study drug. The majority of the AEs were mild in severity and were considered drug-related. Transient mild or moderate headache and mild or moderate myalgia were the most common AEs, reported by 50 (83%) and 32 (53%) of all subjects, respectively. Adverse event incidence was not significantly greater following combination therapy than Aggrenox® alone.

No other notable safety results were identified in this study regarding clinical laboratory, vital signs, ECGs, or physical examination. Overall, the co-administration of Aggrenox® twice daily (BID) plus omeprazole 80 mg QD appeared to be safe and generally well tolerated by this group of healthy male and female subjects in this study.

Conclusions:

The steady-state PK of dipyridamole administered as Aggrenox® BID was unaffected by co-administered omeprazole 80 mg QD or co-administered omeprazole preceded by omeprazole 80 mg QD administered for 7 days.

The steady-state inhibition of platelet aggregation by ASA from Aggrenox® BID was unaffected by co-administered omeprazole 80 mg QD or co-administered omeprazole preceded by omeprazole 80 mg QD administered for 7 days.

Date of Report	18 November 2011