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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00296803
		Study Code:	L_9842
Generic drug name:	Clopidogrel	**Date:**	09/01/ 2008

Title of Study: A Pilot Study to Examine the Effects of Clopidogrel Compared to Placebo on Markers of Inflammation in Subjects with Metabolic Syndrome who are Receiving Background Therapy including Low Dose Aspirin.

Principal Investigator:
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Publications (References):

1. Bhatt et al., NEJM April 20, 2006; 354:1706-1717

Study Initiation/Completion Dates:
Study Start Date with a kick-off meeting: 10 OCT 2005
Protocol Approval: 17 OCT 2005
First Subject Screened: 02 NOV 2005
First Subject Randomized: 06 DEC 2005
Last Subject Visit: 16 AUG 2006

Phase of development:
Phase IV pilot study

Objective:

The study objectives were: to assess the effect of treatment and the difference between treatments with either clopidogrel (75 mg) plus aspirin (81 mg) or placebo plus aspirin (81 mg) on high sensitivity C-reactive protein (hs-CRP), CD40-ligand, soluble P-selectin and N-terminal probrain natriuretic peptide (NT-pro-BNP) in men and women with metabolic syndrome and elevated ($\geq$2.0 mg/L and $\leq$10 mg/L) hs-CRP levels at study baseline on stable medications for the 6 weeks prior to study entry; and to evaluate adjusted mean changes (from baseline) of biomarkers.

Methodology:

PROCLAIM was a multi-center, Phase IV, double-blind, placebo-controlled, randomized trial of clopidogrel 75 mg *vs.* placebo on a background of 81 mg daily aspirin therapy. Subjects participated in the study for a total of 9 weeks. All visits were measured from baseline at Week 0, visit window being +/- 3 days. At Week –2, written informed consent was obtained, a waist circumference measurement taken, vital signs measured and recorded, and blood samples were drawn and processed at the site and then sent to the central laboratory for determination of hematology, and serum chemistries including markers of inflammation and platelet activation. During the 2 weeks of the screening period, after return of qualifying lab results, the subjects returned to the study site to complete the screening process provided their complete medical history, detailing all concomitant medication use, and received a brief medical exam including vital signs. If the subject met all of the inclusion criteria and none of the exclusion criteria, he/she returned for Week 0 Visit.

At Week 0 subjects had vital signs measured, study medication dispensed, and blood samples drawn for the measurement of markers of inflammation and platelet activation. At Week 2 and Week 4 subjects returned for a clinic visit, at which time vital sign measurements were taken, adverse events were assessed and blood samples were drawn to measure markers of inflammation and platelet activation. Study drug compliance and concomitant medication was assessed at each visit to ensure ongoing compliance. Adverse events were queried and recorded. At Week 6 subjects returned to the clinic, study drug was collected and final compliance was verified, a final blood sample was drawn for hematology, serum chemistries, markers of inflammation and platelet activation, and adverse events were assessed. At Week 7 subjects returned for their final study visit. At this time, a brief physical exam including vital signs was done, and adverse events were assessed.

Number of Subjects (planned, randomized, intent-to-treat, per-protocol, completed, analyzed):

Planned/Enrolled: 360 to obtain 218 randomized; Randomized: 181; Intent-to-treat: 181; Completed: 147; Per-protocol: 138; Analyzed: 181

Diagnosis and Main Criteria for Inclusion:

Subjects ≥18 years of age with metabolic syndrome, on stable medications for 6 weeks prior to entry, who met all of the inclusion criteria and have hsCRP values (≥2.0 mg/L and ≤10 mg/L) at screening (Week -2). Subjects that met 3 of the 5 National Cholesterol Education Program (NCEP) criteria were classified as having metabolic syndrome. The NCEP criteria were: Triglycerides ≥150 mg/dL; SBP ≥130 mmHg; DBP >85 mmHg; fasting blood glucose ≥110 mg/dL; waist circumference >101.6 cm (40 inch) for men and >88.9 cm (35 inch) for women; and HDL cholesterol <40 mg/dL for men, and <50 mg/dL for women.

Test Product, Dose and Mode of Administration: Clopidogrel bisulfate 75 mg plus aspirin 81 mg tablets given orally.

Reference Therapy, Dose and Mode of Administration: Placebo plus aspirin 81 mg tablet given orally. Placebo matched to clopidogrel in color and size.

Duration of Treatment: Maximum study duration for an individual was 9 weeks; 2 weeks screening and 6 weeks on active treatment and a final visit 1 week after last dose.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint or set of endpoints was the change from baseline at the end of Week 6 in four biomarkers of inflammation. The change from baseline in hs-CRP, CD40-ligand, soluble P-selectin, and NT-pro-BNP was expressed as the mean median, and mode of individual values measured from study start (average of Week -2 and Week 0) to end of Week 6 (average of Week 4 and Week 6). Biomarker levels were calculated separately for each treatment arm. A secondary outcome measure of a weighted composite as described in the protocol was not constructed or evaluated (See Section 10.2, Protocol Deviations). However, the difference between treatment groups on adjusted mean changes from baseline regarding hs-CRP, CD40-ligand, soluble P-selectin and NT-pro-BNP was evaluated.

Safety:

The primary safety endpoint or set of endpoints was the adverse events and/or serious adverse events reported at each clinic visit. Additional safety endpoints included those associated with scheduled physical examinations, vital signs and scheduled clinical laboratory assessments done at Screening (Week -2) and at the end of drug treatment phase (Week 6) and a brief physical examination performed at Week 7. Vital signs included temperature, heart rate, systolic and diastolic blood pressure and respiration rate.

Pharmacokinetics: Pharmacokinetic parameters were not evaluated.

Pharmacokinetic/Pharmacodynamic Relationships: Pharmacokinetic/pharmacodynamic relationships were not examined.

Statistical Methods: Statistical analyses were conducted to address the study objectives. An intention-to-treat (ITT) principle was employed for estimation of the study endpoints.

Selected variables were summarized using means, standard deviations, medians, and ranges. Counts and percentages were employed to summarize nominal and categorical level data. Parameter estimates for the primary endpoints and associated variances were calculated. Bias corrected bootstrap confidence intervals were calculated employing the 2.5% and 97.5% percentiles using the results of 1,000 bootstrap (unrestricted) samples. Graphics were employed with interval and ratio endpoints to visually examine the distribution by treatment arm and for comparisons of treatment arms.

ITT subjects were used for the efficacy analyses. Efficacy variables were also analyzed in the per protocol (PP) populations. Safety analysis was performed on a safety population that included all subjects enrolled in the study. The Safety population is defined as subjects who are randomized to a treatment arm, and where randomization is considered complete when the subject is assigned a trial number (subject number)..

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary and secondary efficacy analyses were performed to obtain point estimates of arithmetic mean change scores for the biomarkers of inflammation, hsCRP, CD40-ligand, soluble P-selectin, and NT-pro-BNP separately for each arm. Point estimates of change scores for individual treatment arms resulted in no statistically significant changes from baseline for any of the four biomarkers in the primary efficacy analysis (changes from baseline to Week 6). However, in a secondary efficacy analysis in which treatment group comparisons were conducted, a statistically significant reduction of CD40-ligand was observed in the clopidogrel plus aspirin group compared to the placebo plus aspirin group (intent-to-treat population, $p = 0.0192$, 95% CI of -342.32 to -30.78; per protocol population, $p = 0.0541$, 95% CI of -353.75 to -3.11). There was a reduction in P-selectin favoring the clopidogrel plus aspirin group although it did not reach statistical significance (ITT population, $p = 0.1636$, 95% CI of -13.47 to 2.30).

The data obtained in this study suggests further exploration of the use of clopidogrel plus aspirin treatment in reducing levels of biomarkers of inflammation.

SAFETY RESULTS:

Safety analyses were performed on the ITT population. There were no deaths, serious adverse events, or other significant adverse events in this study. The most commonly reported of the 89 total AEs in both treatment groups were gastrointestinal disorders and infections.

PHARMACOKINETICS:

Pharmacokinetic parameters were not evaluated.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Pharmacokinetic/pharmacodynamic relationships were not assessed.

Date of Report: 27 AUGUST 2007 (Final Version 1.00)