| *These results are supplied for informational purposes only.*<br>*Prescribing decisions should be made based on the approved package insert in the country of prescription* | | | |
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| **Sponsor/company:** | Bristol-Myers Squibb and Sanofi-Aventis | **ClinicalTrials.gov Identifier:** | NCT00360386 |
| | | **Study Code:** | C_9108 |
| **Generic drug name:** | Clopidogrel | **Date:** | 18/01/2008 |

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| **Title of the study:** | **A**ssessment of the best **L**oading dose of clopidogrel to **B**lunt platelet activation, **I**nflammation and **O**ngoing **N**ecrosis | |
| **Principal investigator:** | Prof. Gilles Montalescot | |
| **Study centre(s):** | Seven (7) centres in the Paris region | |
| **Publications:** | None | |
| **Study period:**<br>**Date first patient enrolled:**16/03/2004<br>**Date last patient completed:** 02/02/2005 | | **Phase of development:** II |
| **Objectives:** | **Primary:** to compare the kinetics of platelet aggregation inhibition (aggregometry) and platelet activation (flow cytometry) with different loading doses of clopidogrel.<br>**Secondary:** to evaluate the impact of these three loading doses on various parameters of inflammation and necrosis, and their safety . | |
| **Methodology:** | Three-arm, randomised open-label trial comparing three doses of clopidogrel (300 mg, 600 mg, and 900 mg) with a blind centralized evaluation | |
| **Number of patients:**<br>**Evaluated:** | Planned: 103; randomised: 103; treated: 103<br>Efficacy: 90; safety: 103 | |
| **Diagnosis and criteria for inclusion:** | Ischemic symptoms (onset < 48 hours), treated at hospital admission with oral or intravenous aspirin (250-500 mg) and subcutaneous low molecular weight heparin (at the dosage approved for acute coronary syndrome) | |
| **Investigational product:**<br>Dose:<br>Administration: | Clopidogrel<br>Single dose of 300 mg, 600 mg or 900 mg<br>Commercially available 75 mg tablets p.o. | |
| **Duration of treatment:**<br>Single dose | | **Duration of observation:**<br>24 h and for 1 month after hospital discharge |
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| **Reference therapy:** | None |
| Dose:<br><br>Administration: | NA<br><br>NA |
| **Criteria for evaluation:**<br><br>Safety: | <br><br>All adverse events, bleeding events, gastrointestinal events (vomiting, diarrhoea, dyspepsia), platelet count, white blood cell count (including neutrophils), haemoglobin, ASAT and ALAT |
| **Pharmacodynamic sampling times and bioanalytical methods:** | Baseline (0 h), 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 24 h<br><br>Platelet aggregometry and flow cytometry |
| **Statistical methods:** | One-way ANOVA, one-way ANCOVA, repeated measures mixed model ANOVA, log-rank test, Hodhe Lehmann estimator, Kaplan-Meier survival curves, O'Brien test, and Fisher's exact probability test |
| **Summary:**<br><br>Efficacy results: | <br><br>Clopidogrel 600 mg and 900 mg were consistently found to be more effective than 300 mg in increasing the platelet aggregation inhibition intensity after activation by ADP 5 µmol/l. Maximum aggregation inhibition $E_{max}$ was significantly greater after clopidogrel 600 mg and 900 mg dosages than 300 mg. Although there were no dosage differences in times to reach $E_{max}$, time to reach 30% inhibition occurred earlier after both clopidogrel 600 mg and 900 mg dosages, as compared to 300 mg, and was followed by longer durations of inhibition. The level of inhibition reached in 5 hours after a 300-mg clopidogrel loading dose was obtained in only 2 hours following administration of both 600-mg and 900-mg clopidogrel loading doses. Both $AUC_{0-6\ h}$ and $AUC_{0-24\ h}$ values of maximum platelet aggregation inhibition decreased significantly after clopidogrel 600 mg and 900 mg, compared to 300 mg. There were no effects of clopidogrel on the velocity of platelet aggregation, but aggregation at 2 minutes was inhibited more effectively by clopidogrel 600 mg and 900 mg, than by 300 mg.<br><br>Similar significant results were obtained for corresponding effects of clopidogrel, when aggregation was induced by ADP 20 µmol/l.<br><br>The O'Brien test confirmed that the clopidogrel 600 mg and 900 mg were associated with significant effects on aggregation intensity $AUC_{0-6\ h}$ and $AUC_{0-24\ h}$ values, aggregation inhibition $AUC_{0-6\ h}$ and $AUC_{0-24\ h}$ values, as well as times to reach 30% aggregation inhibition.<br><br>Flow cytometry results confirmed the superiority of both clopidogrel 600 mg and 900 mg over 300 mg in inhibiting platelet aggregation.<br><br>However, there were no statistically significant effects of clopidogrel dosages on inflammation parameters or tissue necrosis parameters.<br><br>Six (6) MACEs were reported: four (4) occurred in the 300-mg cohort, two (2) in the 600-mg cohort, and none in the 900-mg cohort. |

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| Safety results: | In total, 130 adverse events occurred by the end of the one month follow-up period and at least one adverse event was experienced by 65 patients (63%). Adverse events included 40 events in 23 patients from the 300-mg group, 30 events in 17 patients from the 600-mg group, and 60 events in 25 patients from the 900-mg group.<br><br>A total of 15 patients (15%) experienced 18 serious adverse events. Respectively 8, 3, and 7 serious adverse events were reported in the 300-mg, 600-mg, and 900-mg cohorts. Only 4 of these serious adverse events, affecting 4 patients, were considered as related to clopidogrel. All were mild or moderate bleedings according to GUSTO classification.<br><br>Bleedings comprised 34% of all adverse events (44/130) at one month and were experienced by 35% of patients (36/103). Respectively 12, 10, and 14 patients experienced at least one bleeding in the 300-mg, 600 mg, and 900 mg cohorts.<br><br>Laboratory variables showed either no abnormality or non-serious changes which returned to normality at the final follow-up visit.<br><br>All adverse events resolved during the course of the study. No patient died and none was withdrawn from the study for an adverse event. |
| **Date of report:** | 27th March 2006 |