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Sponsor/Company: sanofi-aventis **Drug substance**: SR25990 (clopidogrel)	**Study Identifier**: NCT00386191 **Study code**: SFY6913

Title of the study:

Evaluation of the safety and efficacy of clopidogrel sulfate 50 mg and clopidogrel sulfate 75 mg for the treatment of cerebral infarction (Multicenter, randomized, double-blind, comparative study)

Study center(s): National, multicenter study with 118 active centers in Japan.

Study period:

Date first subject/patient enrolled: 04-Sep-2006

Date last subject/patient completed: 12-Dec-2008

Phase of development: Phase 4 (post-marketing study)

Objectives:

The primary objective of this study was to compare the safety of clopidogrel sulfate 50 mg and clopidogrel sulfate 75 mg for the treatment of cerebral infarction using the incidence of bleeding adverse events (AEs) as the primary safety variable.

The secondary objectives were to demonstrate the safety of clopidogrel sulfate 50 mg and clopidogrel sulfate 75 mg for the treatment of cerebral infarction using incidences of serious adverse events (SAEs), serious bleeding AEs AEs (leukopenia, neutropenia, thrombocytopenia and hepatic dysfunction) as secondary variables, and to demonstrate the efficacy of clopidogrel sulfate 50 mg and clopidogrel sulfate 75 mg for the treatment of cerebral infarction using the incidence of vascular events as secondary variables.

Methodology:

National, multicenter, randomized, double-blind, comparative, Phase IV study

Number of subjects/patients:

Planned:	1100 (550 in the 50mg group and 550 in the 75mg group)
Screened:	1110 (558 in the 50mg group and 552 in the 75mg group)
Randomized:	1110 (558 in the 50mg group and 552 in the 75mg group)
Treated:	1108 (556 in the 50mg group and 552 in the 75mg group)
Efficacy:	1110 (558 in the 50mg group and 552 in the 75mg group)
Safety:	1110 (558 in the 50mg group and 552 in the 75mg group)

Diagnosis and criteria for inclusion:

Patients between 20 and 74 years of age, a body weight >50kg with an episode of cerebral infarction (excluding cardiogenic cerebral thromboembolism) occurring at least eight days prior to randomization and for whom the clinical course up to randomization had been well documented and confirmed by diagnostic brain imaging, computed tomography (CT) or magnetic resonance imaging (MRI).

Investigational product: clopidogrel sulfate 25mg tablets and clopidogrel sulfate 75mg tablets

Dose: 50mg and 75mg

Administration: oral, once daily after a meal

Reference therapy: Placebo tablets matching the clopidogrel sulfate 25mg tablets and clopidogrel sulfate 75mg tablets

Administration: oral, once daily after a meal
Duration of treatment and observation: Treatment and observation duration was 52 weeks.
Criteria for evaluation:
Safety: The primary safety endpoint was bleeding AEs (AEs with any bleeding) and the main secondary endpoints were SAEs, bleeding SAEs (all bleeding AEs that met the criteria for SAE) and AEs (leukopenia, neutropenia, thrombocytopenia, and hepatic dysfunction). Efficacy: The efficacy endpoint was vascular events (cerebral infarction, myocardial infarction, other vascular deaths, and other vascular events).
Statistical methods:
Analysis population: The main safety analyses and all efficacy analyses were based on the intent-to-treat (ITT) population as randomized treatment and were defined as all randomized patients. Other safety analyses were based on the all treated population. Analyses of primary variable: For the time from randomization to the first occurrence of a bleeding AE, comparisons between clopidogrel sulfate 50 mg and 75 mg were performed using a Log-rank test with a two-sided 5% significant level (primary analysis in this study). Cumulative incidence functions with 95% confidence intervals (CI) were estimated with the Kaplan-Meier technique and Greenwood's formula. The hazard ratio (50 mg group/75 mg group) with 95% CI was estimated using Cox model with treatment group as the factor. Analyses of secondary variables: Log-rank tests and estimations of cumulative incidences and hazard ratios were performed for the time to first occurrence of any secondary event analyzed, in a manner similar to the analysis of primary safety variable.
Other safety analyses: Treatment-emergent AEs (TEAEs) were defined as AEs that developed or worsened under treatment from the first investigational product (IP) intake to 14 days after the last IP intake. The frequency distributions of patients with TEAEs, serious TEAEs and TEAEs leading to treatment discontinuation were summarized by treatment. For central laboratory parameters and vital signs, raw values and their changes from baseline across visits were summarized by treatment group. The number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormalities (PCSAs) in the on-treatment period were summarized by parameter in each treatment group.
Summary:

Safety results:

Primary endpoint (ITT population):

No statistically significant difference between treatment groups was observed for the primary endpoint, bleeding AEs (p=0.2274, Log-rank test). The cumulative incidences of bleeding AEs at Week 52 in the 50mg and 75mg groups were 14.0% and 16.5%, respectively, and the hazard ratio for the 50mg group was 0.831 (95% CI: 0.615 to 1.124).

Main secondary endpoints (ITT population):

Serious adverse events:
No statistically significant difference between treatment groups was observed (p=0.5035, Log-rank test). The cumulative incidences of SAEs at Week 52 in the 50mg and 75mg groups were 8.6% and 9.5%, respectively, and the hazard ratio for the 50 mg group was 0.877 (95% CI: 0.597 to 1.289).

Serious bleeding adverse events:
No statistically significant difference between treatment groups was observed (p=0.6496, Log-rank test). The cumulative incidences of serious bleeding AEs at Week 52 in the 50mg and 75mg groups were 1.7% and 1.5%, respectively, and the hazard ratio for the 50mg group was 1.240 (95% CI: 0.489 to 3.142).

Adverse events of leukopenia, neutropenia, thrombocytopenia and hepatic dysfunction:
No statistically significant difference between the treatment groups was observed (p=0.5834, Log-rank test) for AEs related to leukopenia, neutropenia, thrombocytopenia and hepatic dysfunction. The cumulative incidence at Week 52 was 22.4% in the 50mg group and 23.8% in the 75mg group, and the hazard ratio for the 50mg group was 0.935 (95% CI: 0.735 to 1.190). Individually there were no significant differences between the groups in the incidences of leukopenia, neutropenia, thrombocytopenia and hepatic dysfunction.

Other safety endpoints (all treated population):
There was no significant difference in TEAEs between treatment groups (all treated population) and no significant difference in the preferred term (PT) class of serious TEAEs between treatment groups.

Efficacy results:

No statistically significant difference between treatment groups was observed for vascular events (p=0.4118, Log-rank test). The cumulative incidences of vascular events at Week 52 in the 50mg and 75mg groups were 3.8% and 2.6%, respectively, and the hazard ratio for the 50mg group was 1.312 (95% CI: 0.685 to 2.514).

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