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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00325390
Drug substance(s):	clopidogrel (SR25990C)	**Study Code:**	EFC6720 (DV7314-26)
		Date:	12 March 2007

Title of the study:	Double-blind parallel comparison study of SR25990C versus standard therapy in Japan (ticlopidine) in patients with acute coronary syndrome without ST-segment elevation who are planned for percutaneous coronary intervention (PCI).
Investigator(s):	Shinya Goto, M.D., Dr. of Med Sci, Associate Professor of Medicine, Division of Cardiology, Department of Medicine, Tokai University School of Medicine
Study center(s):	105 centers in Japan
Publications:	None
Study period: Date first patient/subject enrolled: 2 July 2004 Date last patient/subject completed: 25 August 2005	**Phase of development:** Phase III
Objectives:	The primary objective was to assess the safety and efficacy of SR25990C (loading dose: 300 mg, maintenance dose: 75 mg/day) in comparison with standard therapy in Japan (ticlopidine) in patients with acute coronary syndrome without ST-segment elevation and planned for PCI (including stenting).
Methodology:	Multicentre, randomized, double blind, two parallel group trial of SR25990C versus ticlopidine on background therapy of aspirin.
Number of patients:	Planned: 800 patients (400 in each treatment group) Randomized: 802 patients (SR25990C: 402, ticlopidine: 400)
Diagnosis and criteria for inclusion:	Patients aged above 20, admitted to hospitals with symptoms suspected to represent an acute coronary syndrome without ST-segment elevation (unstable angina and acute myocardial infarction without ST-segment elevation) who are planned for PCI (including stenting).

Investigational product: Dose: Administration:	SR25990C (clopidogrel sulfate) Four tablets of SR25990C 75 mg (300mg) and 1 tablet of ticlopidine placebo were to be administered as soon as possible after randomization. If the initial dose was administered in the morning, then as a rule 1 tablet of ticlopidine placebo was to be administered after dinner. From Day 2 to Day 28, 1 tablet of SR25990C 75mg once daily after breakfast, and 1 tablet of ticlopidine placebo twice daily, after breakfast and dinner, were to be administered. Tablet of aspirin 81-100 mg/day was to be administered as background therapy.
Duration of treatment: 28 days	**Duration of observation:** 28 days
Reference therapy: Dose: Administration:	ticlopidine hydrochloride Four tablets of SR25990C placebo and 1 tablet of ticlopidine 100mg were to be administrated as soon as possible after randomization. If the initial dose was administered in the morning, then as a rule 1 tablet of ticlopidine 100mg was to be administered after dinner. From Day 2 to Day 28, 1 tablet of SR25990C placebo once daily after breakfast as a rule, and 1 tablet of ticlopidine 100mg twice daily, after breakfast and dinner, were to be administered. Tablet of aspirin 81-100 mg/day was to be administered as background therapy.
Criteria for evaluation:	
Safety:	<u>Primary safety endpoint:</u> Incidence of safety events An incidence during 28 days, including the occurrence of any of the followings (1) Clinically significant bleeding (excluding puncture site bleeding whose casual relationship can be ruled out) (2) Blood disorder (leukopenia, neutropenia or thrombocytopenia occurring as adverse drug reaction) (3) Elevated liver function values [ALT (GPT), γ-GTP, ALP or total bilirubin elevated by 50% or more compared with baseline (excluding changes within normal ranges) and occurring as adverse drug reaction] (4) Permanent study drug discontinuation due to skin disorders, gastrointestinal disorders, bleeding, hepatic disorders, or significant decreases in such tests as leukocytes, neutrophils or platelets occurring as adverse drug reaction <u>Secondary safety endpoints:</u> Incidence of adverse events Incidence of adverse drug reactions Incidence of bleeding events
Efficacy:	<u>Primary efficacy endpoint:</u> Incidence of efficacy events An incidence during 28 days, including the occurrence of any of the followings (1) All-cause mortality (2) Acute myocardial infarction (3) Revascularization (excluding revascularization planned as a result of the first coronary angiography after the visit) <u>Secondary efficacy endpoint:</u> Incidence of safety event or efficacy event

Statistical methods:	(1) Incidence of safety events The SR25990C group and the ticlopidine group are compared for the incidence of safety events observed up to 28 days after the first drug intake. Pearson's Chi-squared test is performed at the 5% significance level (two-sided) and the two-sided 95% confidence interval for the difference in incidence between two groups is calculated. Furthermore, as post hoc analysis after the blind was broken, the Cochran-Mantel-Haenszel test was applied for comparison between the the two groups adjusting the influences of "CABG based on initial CAG" considered to be an important prognostic factor influential on safety events. (2) Incidence of efficacy events The two-sided 95% confidence interval for the difference between the SR25990C group and the ticlopidine group is calculated for the incidence of efficacy events observed up to 28 days after the first drug intake.
Summary:	
Data sets analyzed:	Intent to Treat (ITT) population: 799 patients (SR25990C: 400, ticlopidine:399) Per Protocol Set (PPS): 661 patients (SR25990C: 328, ticlopidine:333) Modified PPS: 744 patients (SR25990C: 371, ticlopidine:373)
Safety results:	In the primary safety analysis using the ITT population, the incidence of safety events was 24.25% (97/400) in the SR25990C group and 29.57% (118/399) in the ticlopidine group (Pearson's Chi-squared test: p = 0.0898). There was no statistically significant difference between the two groups. The point estimate of difference between the two groups for incidence (ticlopidine – SR25990C) was 5.32% (two-tailed 95% confidence interval: −0.82 to 11.46%). There was a significant difference in the modified PPS (Pearson's Chi-squared test: p = 0.0352) and the incidence of safety events was lower in the SR25990C group than in the ticlopidine group (In PPS, Pearson's Chi-squared test: p = 0.0602). However, in any of the ITT, modified PPS and PPS populations, the incidence of safety events was consistently lower in the SR25990C group than in the ticlopidine group. As a result of post hoc analysis after the blind was broken, logistic regression analysis suggested that "CABG based on initial CAG" was a factor with a strong influence on safety events. Then, the Cochran-Mantel-Haenszel test, adjusted for this factor, was performed. As a result, it was shown that the incidence of safety events was significantly lower in the SR25990C group than in the ticlopidine group (p=0.0358).
Efficacy results:	In the primary efficacy analysis using the ITT population, the incidence of the efficacy events was 10.25% (41/400) in the SR25990C group and 9.52% (38/399) in the ticlopidine group. The point estimate of difference between the two groups for incidence (ticlopidine-SR25990C) was -0.73% (two-tailed 95% confidence interval: -4.87 to 3.41%). The two-tailed 95% confidence interval included zero, so the incidence of efficacy events was considered to be comparable between the two groups.
Date of full report:	13 December 2006