SYNOPSIS

Name of company: sanofi-aventis **Name of finished product:** **Name of active substance(s):** Otamixaban	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** **Volume:** **Page:**	**(For National Authority Use only)**
Title of the study:	The SEPIA-PCI Trial. A multinational, randomized, double-blind, double-dummy, exploratory, parallel-group, dose-ranging phase II Study to Evaluate the Pharmacodynamics, the safety and tolerability, and the pharmacokinetics of several Intravenous regimens of the factor Xa inhibitor otamixAban (XRP0673), in comparison to intravenous unfractionated heparin, in patients undergoing non-urgent Percutaneous Coronary Intervention (XRP0673A/2002; DRI6199)	
Investigator(s):	[redacted]	
Study center(s):	Patients were treated at 76 study centers in 10 countries: Belgium (2), Canada (9), Czech Republic (3), France (5), Germany (14), the Netherlands (6), Slovakia (3), South Africa (2), Spain (6), USA (26) One additional US center randomized a single patient, who was however not treated.	
Publications (reference):	Not yet published at time of preparation of this study report	
Study period: Date first patient enrolled: 24 September 2004 Date last patient completed: 19 October 2005		**Phase of development:** 2b
Objectives:	Primary objectives • to determine the effect of several intravenous (IV) regimens of otamixaban on the pharmacodynamic marker F1+F2 (marker of thrombin generation) at the end of the infusion, as compared to IV unfractionated heparin (UFH) in patients undergoing non-urgent percutaneous coronary intervention (PCI); • to determine the effect of several IV regimens of otamixaban on the pharmacodynamic marker anti-factor Xa (anti-Xa) activity at the end of the infusion in patients undergoing non-urgent PCI Secondary objective: to identify a safe range of dosages of IV otamixaban in comparison to UFH.	
Methodology:	This was a multinational, randomized (stratified according to planned use of glycoprotein (GP) IIb/IIIa inhibitors and country), double-blind, double-dummy, exploratory, dose-ranging study with 6 parallel treatment groups. Eligible patients were randomized (1:1:1:1:1:1) via an interactive voice response system to 1 of 5 otamixaban dosage regimens or UFH. All patients were to receive both Drug A (otamixaban or placebo) and Drug B (UFH or placebo).	

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Number of patients:	Planned: 930	Randomized: 947	Treated: 930
Evaluated:	"Treated with co-primary endpoints" population: 850 Per protocol population 701 Modified intent-to-treat population: 945 Safety population: 930 Pharmacokinetic population: 479		
Diagnosis and criteria for inclusion:	Men or women ≥18 years of age, due to undergo non-urgent PCI (elective, post unstable angina, or post myocardial infarction [MI]) of a single or multiple sites of native vessel(s) during the same procedure with balloon angioplasty (with or without stent) using a femoral approach, and with planned treatment with aspirin and clopidogrel prior to PCI.		
Investigational product:	**Otamixaban**		
Dose:	IV bolus / IV infusion Dose group 1: 0.025 mg/kg / 0.035 mg/kg/h Dose group 2: 0.045 mg/kg / 0.065 mg/kg/h Dose group 3: 0.080 mg/kg / 0.120 mg/kg/h Dose group 4: 0.120 mg/kg / 0.160 mg/kg/h Dose group 5: 0.140 mg/kg / 0.200 mg/kg/h		
Administration:	IV bolus (1 minute) followed by IV infusion (3 hours) Placebo matching otamixaban was used to maintain double-blind conditions.		
Batch number(s):	[redacted]		
Duration of treatment: 3 hours	**Duration of observation:** 31 days • enrollment period: ≤14 days (Day -14 to Day 1); • treatment and hospitalization period: 3 days (including pre-randomization, randomization, index PCI, post-infusion and post-PCI assessments; Day 1 to Day 3 or hospital discharge, whichever came earlier); • follow-up period: 28 days with follow-up visits at Day 14 and (by telephone) at Day 31.		
Reference therapy:	**UFH**		
Dose:	With concomitant GP IIb/IIIa inhibitor use: Initial bolus of 50 to 70 IU/kg, with subsequent bolus(es) of 2000 to 5000 IU, to achieve a target activated clotting time (ACT) of 200 to 300 seconds Without concomitant GP IIb/IIIa inhibitor use: Initial bolus of 70 to 100 IU/kg, with subsequent bolus(es) of 2000 to 5000 IU, to achieve a target ACT of 301 to 350 seconds		
Administration:	IV bolus Placebo matching UFH was used to maintain double-blind conditions.		
Batch number(s):	[redacted]		

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Criteria for evaluation:		
Pharmacodynamics/efficacy:	Primary variables (pharmacodynamics) The study investigated the following two co-primary endpoints: • change in F1+F2 from baseline to end of 3-hour infusion; • anti-Xa activity at end of 3-hour infusion. Tertiary variables (clinical efficacy) • incidence of the composite endpoint of all-cause mortality, MI, or target vessel revascularization (urgent and non-urgent) within 30 days after randomization, based on data adjudicated by the clinical events committee (CEC); • incidence of the mixed efficacy/safety composite endpoint of all-cause death, MI, target vessel revascularization (urgent or non-urgent), and TIMI major or minor bleeding within 30 days after randomization, based on CEC-adjudicated data. Other variables Coagulation parameters (aPTT, PT/INR, RVVT, dPT); inflammation markers (CRP, CD40 ligand, IL-6); markers of thrombin activity (TAT, D-dimer); acute-phase reactant proteins (von Willebrand factor, fibrinogen); cardiac markers: CK-MB, troponin T.	
Safety:	Secondary variables (safety; based on CEC-adjudicated data; primary time point: Day 3/hospital discharge) • incidence of the composite endpoint of TIMI major, minor and minimal bleeding; • incidence of the composite endpoint of TIMI major and minor bleeding; • incidence of TIMI major bleeding; • incidence of TIMI minor bleeding. Other variables Stroke (CEC-adjudicated); adverse events (AEs) reported by the patient or noted by the Investigator; laboratory safety data (hematology, clinical chemistry, urinalysis); 12-lead electrocardiogram	
Pharmacokinetics:	Otamixaban plasma concentrations at predefined time points, including the concentration at 1 minute after the end of the 1-minute bolus dose of Drug A (C_{1min}) and the concentration at the end of infusion (C_{eoi}).	
Pharmacokinetic sampling times and bioanalytical methods:	Sampling times: predose, 1 minute (end of IV bolus), end of PCI, end of infusion, and at 30 minutes, 1, 2, 4, 8, and 24 hours after end of infusion. Concentrations of otamixaban were measured using a combined liquid chromatography and mass spectroscopy method. The lower limit of quantitation was 1 ng/mL (assay range: 1 to 500 ng/mL).	
Statistical methods: Analysis populations:	• treated with co-primary endpoints population: all patients randomized who had begun treatment with study medication and had data for at least 1 co-primary endpoint at the end of infusion. Patients analyzed as treated; • modified intent-to-treat (mITT) population: all patients randomized who had data for clinical status at Day 3 or 31. Randomized and treated patients were analyzed as treated. Patients randomized but not treated were analyzed as randomized;	

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	• per protocol population: all patients in the "Treated with co-primary endpoints" population who did not have a major protocol deviation; • safety population: all patients randomized who had begun treatment with study medication. Patients analyzed as treated; • pharmacokinetic (PK) population: all patients from PK sites that were treated with otamixaban.	
Analyses of primary variables (pharmacodynamics):	Unless otherwise specified, analyses of the primary variables were performed on the "Treated with co-primary endpoints" population. The primary analysis of F1+F2 compared each otamixaban dosage group with UFH with regard to change in F1+F2 from baseline to the end of infusion using, after rank transformation, an analysis of covariance model that included factors for GP IIb/IIIa inhibitor planned use, treatment group, and ranked baseline F1+F2 value. The primary analysis of anti-Xa activity compared anti-Xa activity at the end of infusion for each of the otamixaban dosage groups 5 to 2 with that for the lowest otamixaban dosage group (group 1), performed after a rank transformation of the variable, using an analysis of variance model that included a factor for GP IIb/IIIa inhibitor planned use and treatment group. The two primary hypotheses were each tested at a 2-sided significance level of 2.5%. A step-down procedure was followed to adjust the alpha level for multiplicity. For both analyses, the estimator of Hodges-Lehman of the difference in median between the respective treatments, with its 95% confidence interval, was displayed.	
Analyses of secondary variables (safety):	The incidence of TIMI bleeding endpoints up to Day 3/hospital discharge was compared between UFH and each otamixaban dosage, controlling for the planned (or actual) use of GP IIb/IIIa inhibitors, using a Cochran-Mantel-Haenszel test in the safety population. The Cochran-Armitage test for dose trend was performed.	
Analyses of tertiary variables (clinical efficacy):	Analyses of clinical efficacy endpoints were performed on the mITT population, analyses of the mixed efficacy/safety endpoint on the safety population. The incidence of the tertiary variables was compared between each otamixaban dosage and UFH, controlling for the planned (or actual) use of GP IIb/IIIa inhibitors, using a Cochran-Mantel-Haenszel test. The Cochran-Armitage test for dose trend was performed.	
Safety analyses:	All safety analyses were carried out on the safety population. Adverse event data was summarized by system organ class and preferred term. Clinical laboratory data was analyzed as descriptive statistics of change from predose and using predefined criteria to identify potentially clinically important individual changes. Electrocardiogram data was analyzed using shift tables.	
Pharmacodynamic analyses:	Analyses of pharmacodynamic variables other than the primary variables were presented using descriptive statistics.	
Pharmacokinetic analyses:	Otamixaban plasma concentrations at each individual time point were tabulated using descriptive statistics for each dosage group.	

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Interim analyses:	The independent data monitoring committee conducted two formal unblinded interim safety analyses during the study (committee meetings in March and June 2005, after 131 and 483 patients respectively had been randomized). After both interim analyses, the committee recommended that the study should continue as planned.	
Summary:	The following table summarizes the most important study findings.	

	Ota.:Dose 1	**Ota.:Dose 2**	**Ota.:Dose 3**	**Ota.:Dose 4**	**Ota.:Dose 5**	**UFH**
F1+F2 (nmol/L) change from baseline to EOI - median	-0.2 (N=126)	-0.3 (N=131)	-0.2 (N=132)	-0.2 (N=124)	-0.3 (N=129)	-0.2 (N=123)
Comparison vs UFH	*ND*	*ND*	*ND*	*p=0.119*	*p=0.008*	
Anti-Xa activity (ng/mL) at EOI - median	65 (N=132)	155 (N=143)	393 (N=144)	571 (N=138)	691 (N=142)	–
Comparison vs dose 1		*p<0.001*	*p<0.001*	*p<0.001*	*p<0.001*	–
Median aPTT (sec) at EOI	42 (N=123)	46 (N=128)	61 (N=133)	68 (N=125)	81 N=123)	72 (N=111)
TIMI major/minor/minimal hemorrhage at Day 3/hospital discharge (N pts)	37 (24.8%) (N=149)	65 (42.2%) (N=154)	66 (41.8%) (N=158)	77 (49.7%) (N=155)	86 (55.1%) (N=156)	59 (37.3%) (N=158)
Comparison vs UFH	*p=0.018*	*p=0.402*	*p=0.410*	*p=0.030*	*p=0.002*	
TIMI major/minor hemorrhage at Day 3/hospital discharge	3 (2.0%) (N=149)	3 (1.9%) (N=154)	6 (3.8%) (N=158)	6 (3.9%) (N=155)	4 (2.6%) (N=156)	6 (3.8%) (N=158)
Triple composite efficacy endpoint (death, MI, or target vessel revasc. up to Day 30 (N pts)	9 (5.8%) (N=155)	11 (7.1%) (N=155)	6 (3.8%) (N=159)	4 (2.5%) (N=159)	8 (5.1%) (N=157)	9 (5.6%) (N=160)
Comparison vs UFH	*p=0.948*	*p=0.601*	*p=0.431*	*p=0.150*	*p=0.834*	
Median otamixaban C_{eoi}	62.0 (N=95)	159.0 (N=84)	373.5 (N=88)	549.0 (N=92)	706.0 (N=94)	–

EOI=End of infusion; ND=Not done, per prespecified hierarchical analysis

Efficacy/pharmacodynamic results:	F1+F2. Only the highest investigated dose of otamixaban (0.140 mg/kg bolus + 0.200 mg/kg/h infusion) produced a significantly greater reduction in F1+F2 than UFH between baseline and the end of infusion (p=0.008). This finding appeared to be driven by the group of patients who received a GP IIb/IIIa inhibitor. Anti-Xa activity. There was a significant dose response across the otamixaban dose groups with respect to anti-Xa activity (p<0.0001 for all comparisons to group 1). Other pharmacodynamic variables. A dose-related effect of otamixaban was observed on coagulation markers (aPTT, INR, dPT, RVVT). The pharmacodynamic effect of otamixaban was observed rapidly as early as 1 min. Minimal change in aPTT was observed at dose 1. At other doses, aPTT returned to baseline (<50 seconds in >75% of patients) within 30 minutes (dose 2) to 4 hours (dose 5) after end of infusion.

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	Clinical efficacy. No dose response was observed for otamixaban in the analyses of the composite clinical efficacy endpoint of all-cause death, MI or target vessel revascularization up to Day 30. No significant difference was detected between any dose of otamixaban and UFH for this endpoint. However, the study was not powered to show such differences.	
Safety results:	Hemorrhagic AEs. A significant dose effect was observed across the otamixaban dose groups for the composite endpoint of TIMI major, minor or minimal hemorrhage up to Day 3/hospital discharge. There were significantly fewer TIMI major, minor or minimal bleedings in otamixaban dose group 1 (24.8%), but significantly more in otamixaban dose group 4 (49.7%) and dose group 5 (55.1%), than in the UFH group (37.3%). Almost all the hemorrhagic episodes were TIMI minimal hemorrhages and were observed at the site of vascular access. Only 4 TIMI major hemorrhages were observed up to Day 3/hospital discharge, all instrumental (1 at dose 4, 1 at dose 5, 2 in UFH group). There was no dose effect for the composite endpoint of TIMI major or minor bleeding up to Day 3/hospital discharge. No significant differences were found between the otamixaban groups and UFH for this endpoint (incidence from 1.9% to 3.9% for otamixaban groups, 3.8% for UFH). The majority of thrombolysis in myocardial infarction (TIMI) major and minor bleeding events were related to vascular access sites (2.3% otamixaban pooled, 2.5% UFH). Non-hemorrhagic AEs. The frequency of non-hemorrhagic treatment-emergent AEs (TEAEs) was similar for otamixaban (40.3%) and UFH (39.2%). The most frequently reported types of non-hemorrhagic TEAEs were musculoskeletal and connective tissue disorders, general disorders and administration site conditions, and cardiac disorders. The incidences of cardiac disorders and of general disorders and administration site conditions were similar in otamixaban and UFH patients. Musculoskeletal and connective tissue disorders were reported more frequently in otamixaban patients (11.8%) than in UFH patients (7.6%). This imbalance was mostly due to groin pain, especially in dose groups 4 (5.2%) and 5 (6.4%), consistent with the higher rate of vascular access site hemorrhage in these dose groups. Deaths and other serious AEs. No deaths occurred up to Day 30. After Day 30, 2 otamixaban-treated patients died (both from group 5: 1 x sudden cardiac death, 1 due to cardiac failure). In addition, 1 subject who was randomized but not treated died due to cardiac failure after Day 30. The overall incidence of serious AEs (hemorrhagic or non-hemorrhagic) up to Day 30 was similar for otamixaban (11.7%) and UFH (12.0%), with no notable differences across the otamixaban dose groups. The only serious hemorrhagic AEs reported for more than 0.5% of otamixaban patients up to Day 30 were vessel puncture site hemorrhage (9 patients, 1.2%) and vascular pseudoaneurysm (7 patients, 0.9%). Neither event was reported in the UFH group. The only serious non-hemorrhagic AEs reported for more than 0.5% of otamixaban patients up to Day 30 were related to ischemia or were reports of overdose, the latter without clinical consequences. No hemorrhagic strokes occurred. Two otamixaban patients experienced an ischemic stroke (1 after Day 30); both patients recovered without sequelae.	

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	Discontinuation of study medication due to a TEAE occurred overall in 1.5% of patients, with a higher frequency in otamixaban dose groups 4 and 5 than in the lower otamixaban dose groups or the UFH group, driven by hemorrhage at the vessel puncture site in dose groups 4 and 5.	
	Analyses of laboratory safety and electrocardiogram parameters did not indicate any consistent differences between otamixaban dose groups and UFH.	
Pharmacokinetic results	Patients showed otamixaban plasma concentrations as expected for their assigned dosing regimen based on modeling and simulation (median C_{eoi} values within 20% of predicted values). Otamixaban plasma concentrations increased with dose. There was a close and direct linear relationship between otamixaban plasma concentrations and pharmacodynamic effect (anti-Xa activity, aPTT, INR, dPT, and RVVT) in the anticipated clinical concentration range up to ~2000 ng/mL of otamixaban.	
Conclusions:	[redacted]	
Date of report:	12 December 2006	