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Sponsor/company:	Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00268619
		Study Code:	HOE498_3501
Generic drug name:	Ramipril	**Date:**	08/02/2008

Title of the study:	A placebo-controlled, double-blind, randomized, multicenter study of ramipril 5 and 10 mg capsules and insulin infusion in subjects with unstable coronary syndromes.	
Investigator(s):	Richard Gallo, MD and Pierre Theroux, MD Montreal Heart Institute 5000 Belanger East Montreal, Qc Canada H1T 1C8	
Study center(s):	10 Sites	
Publications (reference):	No Publication	
Study period: Date first patient enrolled: 24-Jun-2004 Date last patient completed: 11-Aug-2005		**Phase of development:** IIIb No Objection Letter received 18 Sept 2003
Objectives:	The co-primary objectives of the study are: • To demonstrate that the acute administration of ramipril will control the inflammation process in patients with high-risk acute coronary syndrome (ACS) as assessed by the highly specific Greactive protein (hsCRP) blood levels • To demonstrate that the normalization of blood glucose levels with intravenous insulin will improve the inflammation process during the acute phase of an ACS as assessed by tumor necrosing factor alpha (TNFa) blood levels	
Methodology:	This was two by two design in which ACS patients were randomized to double-blind ramipril 10 mg or placebo (6 weeks)/ramipril 5 mg (2 weeks) for the first 8 weeks and randomized to open-label intravenous (IV) insulin therapy or conventional therapy for the first 72 hours or until a percutaneous coronary interventions (PCI) or a coronary artery bypass graft surgery (CABG). From weeks 8 to 12 all patients were to receive ramipril 10 mg. Blood was collected at randomization, 72 hours and 6 weeks and frozen to be assayed for hsCRP and TNFa at the conclusion of the study. At 24 weeks a telephone call was made to determine if the subject was alive and had not experienced a myocardial infarction, stroke or urgent intervention for recurrent symptoms.	

Number of Patients:	Planned: 412 patients	Randomized: 78 patients	Treated: 78 patients
Evaluated:	Changes from baseline in hsCRP and TNFa	Safety: Treatment emergent adverse events (TEAEs)	
Diagnosis and criteria for inclusion:	Male and female patients = 18 years presenting within 12 hours after the last episode of chest pain with either accelerating pattern of anginal pain, prolonged or recurrent anginal pain at rest or minimal effort or anginal pain at rest or minimal effort >48 hours after an acute myocardial infarction and electrocardiographic evidence of myocardial ischemia or abnormal cardiac markers while excluding having heart failure, diabetes mellitus requiring insulin therapy, or an active chronic inflammatory disease, auto-immune disease or cancer. This study was stopped when the last patient randomized completed 12 weeks of the study and before all patients reached 24 weeks of follow-up.		
Investigational product:	ramipril	ramipril	insulin
Dose:	5 mg	10 mg	hospital pharmacy
Administration:	qd	qd	as required
Duration of treatment: 12 weeks		**Duration of observation:** 24 weeks	
Reference therapy:	ramipril placebo	conventional therapy	
Dose:	N/A		
Administration:	Qd		
Criteria for evaluation:	The current report is an abbreviated report, and as such, only the safety results are being presented in full. TEAEs were evaluated, and analyzed using descriptive statistics. A TEAE is defined as any new adverse event (AE) or any existing AE which worsened following the first dose of study drug until 7 days following the last dose of study medication		
Statistical methods:	Descriptive statistics using means, medians, standard deviations, and ranges for continuous data and numbers of patients and percentages for categorical data.		

Summary:

Since only 78 of the planned 412 subjects were randomized and treated, this abbreviated format was used to summarize the results. In addition, since the insulin was only used during the first 72 hours, and it was obtained from commercially available supplies in the hospital pharmacy this summary will only report the results with respect to ramipril. The study completion and demographic results with respect to insulin can be found in the attached tables.

Study Completion

Characteristic	Statistic	Ramipril	Placebo
Number of patients	Number	38	40
Withdrawn	Number (%)	19 (50.0)	16 (40.0)
Duration of study drug (days)*	Mean (SD)	71.4 (28.37)	67.5 (28.15)
	Median	84	84
	Range	1 – 97	1 – 92
Duration of follow-up (days)	Mean (SD)	127.0 (55.38)	130.5 (59.67)
	Median	163	168
	Range	2 – 183	2 – 273
Reason for withdrawal			
Adverse event	Number (%)	2 (10.5)	4 (25.0)
Treatment not required	Number (%)	0 (0.0)	1 (6.3)
Death	Number (%)	2 (10.5)	0 (0.0)
Lost to follow-up	Number (%)	2 (10.5)	2 (12.5)
Other	Number (%)	13 (68.4)	9 (56.3)

* - For the first 56 days in the placebo, subjects were receiving placebo, after which they received ramipril

Demography

Characteristic	Statistic	Ramipril	Placebo
Number of patients	Number	38	40
Age (years)	Mean (SD)	61.5 (11.47)	62.8 (11.94)
	Median	60	61
	Range	40 – 89	35 – 83
Males	Number (%)	32 (84.2)	30 (75.0)
Race			
White	Number (%)	38 (100.0)	39 (97.5)
Asian	Number (%)	0 (0.0)	1(2.5)

TEAEs were reported by 34 (89.5%) ramipril treated patients and 37 (92.5%) patients who received placebo. Possibly related TEAEs were reported by 5 (13.2%) ramipril treated patients and 8 (20.0%) patients who received placebo. The most frequently (>3 patients in any treatment group) reported TEAEs are found in the table below.

All Treatment Emergent Events Reported by More than 3 Patients

System Organ Class/Preferred Term	Ramipril	Placebo
Number of patients	38	40

Any Event	*34 (89.5%)*	*37 (92.5%)*
General disorders	17 (44.7%)	19 (47.5%)
Chest pain	15 (39.5%)	14 (35.0%)
Fatigue	4 (10.5%)	3 (7.5%)
Edema peripheral	1 (2.6%)	4 (10.0%)
Nervous system disorders	17 (44.7%)	14 (35.0%)
Headache	9 (23.7%)	7 (17.5%)
Dizziness	8 (21.1%)	8 (20.0%)
Vascular disorders	12 (31.6%)	19 (47.5%)
Hypotension	8 (21.1%)	8 (20.0%)
Hematoma	4 (10.5%)	7 (17.5%)
Hypertension	1 (2.6%)	5 (12.5%)
Gastrointestinal disorders	11 (28.9%)	13 (32.5%)
Nausea	6 (15.8%)	5 (12.5%)
Constipation	1 (2.6%)	4 (10.0%)
Cardiac disorders	9 (23.7%)	14 (35.0%)
Angina pectoris	1 (2.6%)	5 (12.5%)
Skin and subcutaneous tissue disorders	7 (18.4%)	8 (20.0%)
Ecchymosis	5 (13.2%)	5 (12.5%)
Psychiatric disorders	6 (15.8%)	9 (22.5%)
Anxiety	4 (10.5%)	5 (12.5%)
Injury and procedural complications	5 (13.2%)	5 (12.5%)
Post procedural pain	1 (2.6%)	4 (10.0%)
Metabolism and nutrition disorders	3 (7.9%)	9 (22.5%)
Hypoglycemia	2 (5.3%)	6 (15.0%)

Serious TEAEs were reported by 7 (18.4%) treated patients and 7 (17.5%) patients who received placebo. No serious TEAEs was possibly related to study drug. A 78 white male ramipril treated patient went into cardiogenic shock day 4 of treatment and died. This event was not possibly related to study drug. Two (5.3%) ramipril

	treated patients and 2 (5.0%) patients who received placebo had hypoglycemic events that met the definitions for expedited reporting. That is to say that the symptomatic hypoglycemia was secondary to insulin infusion. Two (5.3%) ramipril treated patients and 5 (12.5%) patients who received placebo experienced TEAEs that lead to the discontinuation of study drug.
Date of report:	30 November 2007

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACS	Acute coronary syndrome
AE(s)	Adverse Event(s)
CABG	Coronary Artery Bypass Graft Surgery
CRF(s)	Case Report Form(s)
hsCRP	Highly specific C-reactive protein
PCI	Percutaneous Coronary Interventions
PCSA	Potentially Clinically Significant Abnormality
SAE(s)	Serious Adverse Event(s)
TEAE(s)	Treatment Emergent Adverse Event
TNFa	Tumor necrosing factor alpha
WHO	World Health Organization