CLINICAL TRIAL PROTOCOL
(Phase III trial)

COMPOUND:
SR141716

Randomized, multinational, multicenter, double-blind, placebo-controlled, two-arm parallel group trial of rimonabant 20 mg OD for reducing the risk of major cardiovascular events in abdominally obese patients with clustering risk factors

STUDY N°:
EFC5826

STUDY NAME:
COMPREHENSIVE **R**IMONABANT **E**VALUATION **S**TUDY OF **C**ARDIOVASCULAR **END**POINTS AND **O**UTCOMES
(CRESCENDO)

VERSION DATE: 3 October 2005

The Sponsor is either ***Sanofi-Synthelabo Recherche*** or other affiliated company of **sanofi-aventis**.

NAMES AND ADDRESSES OF

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CLINICAL TRIAL SUMMARY

COMPOUND: SR141716	STUDY No.: EFC5826
TITLE	**Randomized, multinational, multicenter, double-blind, placebo-controlled, two-arm parallel group trial of rimonabant 20 mg OD for reducing the risk of major cardiovascular events in abdominally obese patients with clustering risk factors**
INVESTIGATOR/TRIAL LOCATION	Prof. Eric J. TOPOL The Cleveland Clinic Foundation 9500 Euclid Avenue CLEVELAND, OHIO 44195, USA Worldwide study
STUDY OBJECTIVES	**Primary objective**: To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of myocardial infarction, stroke, or cardiovascular death in patients with abdominal obesity at increased risk for such cardiovascular events. **Secondary objective**: To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of myocardial infarction, stroke, cardiovascular death, or hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure) in patients with abdominal obesity at increased risk for such cardiovascular events. **Other objectives:** To demonstrate the effect of rimonabant versus placebo on all-cause mortality. To assess the safety of rimonabant in the study population over the duration of the study.
STUDY DESIGN	Multicenter, multinational, randomized, parallel-group, double-blind, controlled trial of rimonabant versus placebo.

CLINICAL TRIAL SUMMARY

COMPOUND: SR141716	STUDY No.: EFC5826
STUDY POPULATION Main selection criteria:	1.Written informed consent obtained 2. Men and women aged 55 or greater, **AND** 3. Presence of abdominal obesity, with a waist circumference greater than 102 cm (40 inches) for males and greater than 88 cm (35 inches) for females on three successive measurements at baseline visit, **AND** 4. Presence of at least one coronary heart disease risk equivalent **OR** two major cardiovascular risk factors (See complete definitions in Section 7.2) Coronary heart disease risk equivalents: a. Recent (within the past 3 years) documented myocardial infarction. b. Stable angina with documented multivessel coronary disease, **and/or** history of multivessel percutaneous coronary intervention or multivessel coronary artery bypass graft surgery c. Recent (within the past 3 years) ischemic cerebrovascular episode. **CT or MRI must have been performed** to document whether a lesion is associated with the ischemic episode and to rule out non-ischemic neurological disease. d. Documented symptomatic PAD (**one of the following primary criteria** must be satisfied): • current intermittent claudication (WHO criteria),**TOGETHER WITH** ankle-brachial index (ABI) equal to or less than 0.85 in either leg at rest, **or** • history of intermittent claudication (WHO criteria) **TOGETHER WITH** either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease. e. Type 2 diabetes mellitus Major cardiovascular risk factors: f. Metabolic syndrome, **as diagnosed by the presence of at least 2 of the following risk factors (if 3 of the risk factors listed below are fulfilled, this is equivalent to two major risk factors and the patient is eligible**): • Elevated fasting triglyceride level • Low HDL-cholesterol level • Impaired fasting plasma glucose • Elevated blood pressure at baseline visit

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	g. Asymptomatic cerebrovascular disease, with greater than 50% stenosis of a carotid, intracranial, and/or vertebral artery, or plaque on IMT, or revascularization h. Renal artery disease, with greater than 60% stenosis of a renal artery or revascularization i. Previous history of abdominal aortic aneurysm repair j. Asymptomatic ABI less than 0.85 k. Elevated hs-CRP greater than 3 mg/L l. Elevated age of 65 years or greater for males and 70 years or greater for females
	Main exclusion criteria • Obesity due to known endocrine disorder, such as hypothyroidism, or hypopituitary or other endocrine disease • Very low-calorie diet (1200 calories or less a day) or bariatric surgery within prior 6 months • Presence of other condition (medical, psychological, social, or geographical) that would either interfere with participation in the trial, lead to inability to complete the trial, or a cardiovascular condition likely to require an invasive intervention within 1 month after randomization • Pregnant or breast-feeding women
Expected number of patients	Approximately 17,000 (8,5 00 per study group)
Expected number of sites:	Approximately 600 active sites (ie, with at least one patient enrolled)
INVESTIGATIONAL PRODUCT(S)	
Formulation(s):	• Tablets for oral administration, containing either 20 mg of active rimonabant, or rimonabant placebo
Route(s) of administration:	• Oral

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Dose regimen:	• Treatment phase [from Day 1 (post-randomization) to Study End Date]: • Group 1 (rimonabant 20 mg): once daily administration in the morning of one tablet containing 20 mg of active rimonabant • Group 2 (rimonabant placebo) once daily administration in the morning of one rimonabant placebo tablet
EVALUATION CRITERIA	Efficacy endpoints: Primary: First occurrence of one of the following Clinical Events Committee-adjudicated events • Any MI, • Any stroke, or • Cardiovascular death Secondary: First occurrence of • Any MI, • Any stroke, • Cardiovascular death, or • Hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure) Other: • All-cause mortality Safety endpoints: All adverse events Heart rate and blood pressure Hematology and biochemistry assessments

CLINICAL TRIAL SUMMARY

COMPOUND: SR141716	STUDY No.: EFC5826
ASSESSMENT SCHEDULE	Baseline: - informed consent completed and signed - check of inclusion and exclusion criteria - medical/surgical history, including neurological and psychiatric history (scripted questions) - physical exam, including detailed neurological assessment - current medications - supine heart rate and blood pressure - height and weight - waist circumference - smoking status - counseling on diet, exercise, and smoking cessation - 12-lead ECG - hematology (Hb,Ht,WBC-diff, platelets) - biochemistry (ALT, AST, ALP, creatinine) - urine pregnancy test (for women of childbearing potential) Treatment phase visits (1-Month, 3-Month, 6-Month visits, then every 6 months until study end): - recording of all primary and secondary efficacy endpoints, if any - recording of AEs, if any - check of study drug compliance - recording of concomitant medications - supine heart rate and blood pressure - physical exam at 6-month visits - 12-lead ECG at penultimate visit - hematology (Hb, Ht, WBC-diff, platelets) at 6-month visits - biochemistry (ALT, AST, ALP, creatinine) at 6-month visits - body weight, at 6-month visits - waist circumference, at 6-month visits

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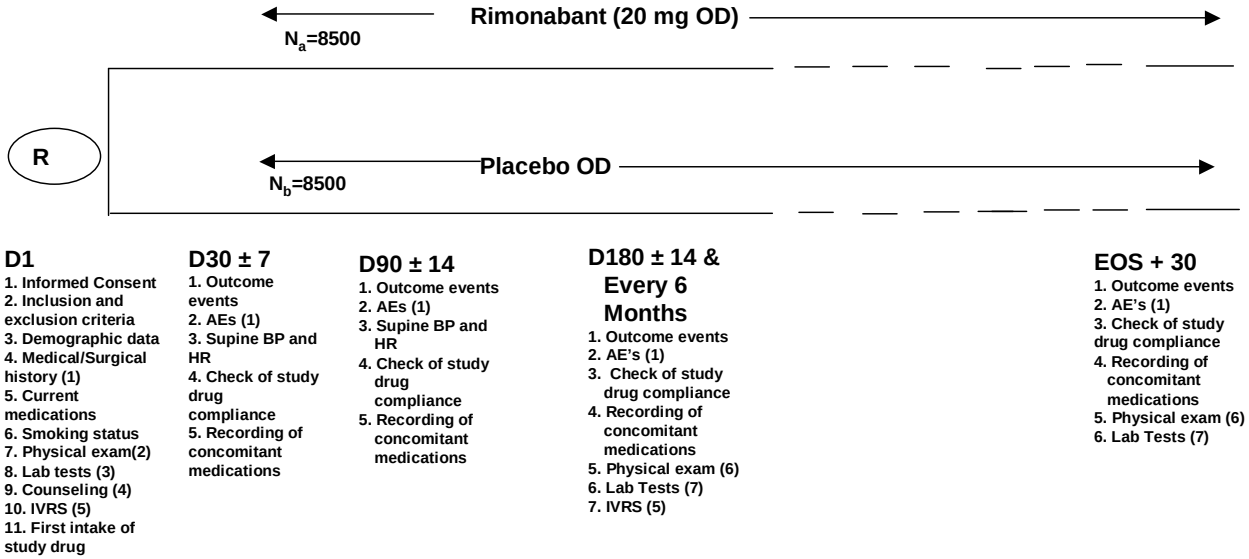
	Treatment phase phone calls (9-Month, then every 6 months, between visits): - recording of all primary and secondary efficacy endpoints, if any - recording of AEs, if any End-of-study visit: - recording of all primary and secondary efficacy endpoints, if any - recording of AEs, if any - check of study drug compliance - recording of concomitant medications - supine heart rate and blood pressure - physical exam - body weight - waist circumference - hematology (Hb, Ht, WBC-diff, platelets) - biochemistry (ALT, AST, ALP, creatinine)
STATISTICAL CONSIDERATIONS	o Intent-to-treat analysis o Survival analysis using a log-rank test on primary efficacy outcome comparing 2 groups with significance level 0.05, 2-sided comparison
DURATION OF STUDY PERIOD (per Patient)	The estimated study duration that served as the assumption for sample size calculations is 50 months. All patients will be followed from randomization until the study end date, which will occur when the last patient has been followed for 33 months, based on 17-month recruitment period.

1. FLOW CHARTS (EFC5826)

Graphical study design



1.	Including specific neurological and psychiatric assessment
2.	Body weight, waist circumference, height measurement, supine HR and BP, detailed neurological exam
3.	Pregnancy test (women of childbearing potential), 12-lead ECG, hematology (Hb, Ht, WBC-diff, platelets), biochemistry (ALT, AST, ALP, creatinine)
4.	Diet, exercise and smoking cessation.
5.	IVRS call for treatment kit number; delivery of corresponding pack of study drug for 6 months treatment
6.	Including body weight, waist circumference, supine BP and HR
7.	Hematology (Hb, Ht, WBC-diff, platelets), biochemistry (ALT, AST, ALP, creatinine)

1.1 Study Flowchart

Evaluation			Treatment and follow-up																
	VISIT	Baseline Visit	1M visit	3M visit	6M visit	9M phone call	12M visit	15M phone call	18M visit	21M phone call	24M visit	27M phone call	30M visit	33M phone call	36M visit	39M phone call[1]	42M visit[1]	45M phone call[1]	48M visit[1]	Final visit[2,3] (end of study)
	Day	Day 1	D30 ±7	D90 ±14	D180 ±14		D360 ±14		D540 ±14		D720 ±14		D900 ±14		D1080 ±14		D1260 ±14		D1440 ±14	D1500 +30
Design																				
Informed consent		X																		
Patient demographics		X																		
Medical / surgical history[4]		X																		
Current medications		X																		
Smoking status		X																		
Inclusion criteria		X																		
Exclusion criteria		X																		
Physical examinations																				
Supine heart rate & blood pressure		X	X	X	X		X		X		X		X		X		X		X	X
Physical exam[5]		X			X		X		X		X		X		X		X		X	X
Body weight		X			X		X		X		X		X		X		X		X	X
Waist circumference		X			X		X		X		X		X		X		X		X	X
Height		X																		
12-lead ECG		X																	X[6]	
Randomization		X																		
Efficacy																				
Efficacy outcomes			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
Treatment																				
IVRS call		X			X		X		X		X		X		X		X		X	
Study drug intake		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
Study drug compliance			X	X	X		X		X		X		X		X		X		X	X
Concomitant medications			X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
Counseling[7]		X																		

[1] If final visit has not been already performed.
[2] Final visit can occur between 33 and 50 months.
[3] Visit may occur up to 30 days after, but never before, the study end date. However, only data up to the study end date should be recorded on CRF.
[4] Including neurological and psychiatric history (scripted questions)
[5] Including detailed neurological exam at baseline.
[6] 12-lead ECG obtained at penultimate (next to last) visit
[7] Dietary counseling, exercise counseling, and smoking cessation counseling, if appropriate.

Laboratory testing																			
Urinary pregnancy test[8]	X																		
Hematology[9]	X			X		X		X		X		X		X		X		X	X
Biochemistry[10]	X			X		X		X		X		X		X		X		X	X
Safety																			
AEs[11]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

[8] For women of childbearing potential only.
[9] Hb, Ht, WBC-diff, platelets
[10] ALT, AST, ALP, creatinine
[11] Including neurological and psychiatric AEs (scripted questions)

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ACC: American College of Cardiology.
AE: Adverse event.
ALP: Alkaline phosphatase.
ALT: Alanine aminotransferase.
AST: Aspartate aminotransferase.
ATP: Adult Treatment Panel.
C5: The Cleveland Clinic Cardiovascular Coordinating Center.
CABG: Coronary artery bypass graft.
CB1: Cannabinoid receptors.
CEC: Clinical Events Committee.
CHD: Coronary heart disease.
CRF: Case report forms.
CT: Computed tomography.
CVD: Cardiovascular death.
DMC: Data Monitoring Committee.
DP: Dorsalis pedis.
DRF: Discrepancy resolution form.
EC: Endocannabinoid system.
ECG: Electrocardiogram.
GCP: Good Clinical Practice.
HbA1c: Hemoglobin A1c.
HDL: High density lipoprotein.
hs-CRP: high sensitivity C-reactive protein.
ICH: International Conference on Harmonization.
IL-6: Interleukin-6.
IMT: Intima-media thickness.
IP: Investigational product.
IRB/EC: Institutional Review Board/Ethics Committee.
ITT: Intent-to-treat.
IVRS: Interactive voice response system.
LDL: Low density lipoprotein.
MedDRA: Medical Dictionary for Regulatory Activities.
MI: Myocardial infarction.
MRI: Magnetic resonance imaging.
NCEP: National Cholesterol Education Program.
OD: Once daily.
OGTT: Oral glucose tolerance test.
PAD: Peripheral arterial disease.
PAI-1: plasminogen activator inhibitor-1. ; Plasminogen activator inhibitor-1.
PCI: Percutaneous coronary intervention.
PCSA: Potentially clinically significant abnormality.

PICH: Primary intracranial hemorrhage.
PSU: Partial shipment unit.
PT: Posterior tibial.
PTA: Percutaneous transluminal angioplasty.
PTCA: Percutaneous transluminal coronary angioplasty.
SAE: Serious adverse event.
sCD40L: Soluble CD40 ligand.
sVCAM-1: Soluble vascular cellular adhesion molecule-1.
ULN: Upper limit of normal range.
WHO: World Health Organization.
WOC: Withdrawal of consent.

4. INTRODUCTION AND RATIONALE

4.1 Role of the metabolic syndrome, caused by insulin resistance, as a determinant of risk for major clinical cardiovascular events

Insulin resistance, a decreased ability of the body's cells to use insulin resulting in impaired glucose control, hyperinsulinemia, activation of the sympathetic nervous system, renal sodium retention, vascular smooth muscle cell proliferation, and vascular hyperreactivity, is one of the earliest abnormalities leading to the cluster of abnormalities that are encountered in the metabolic syndrome, which was first described in 1988 (1). Included among these symptoms are the known cardiovascular risk factors of atherogenic dyslipidemia, elevated blood pressure, elevated glucose, as well as prothrombotic and proinflammatory states (2)(3). Obesity is associated with insulin resistance, and insulin resistance is causally related to the development of both diabetes and hypertension (4)(5)(6). In addition, adipocytes release products that promote other elements of the metabolic syndrome, such as nonesterified fatty acids, which promote a dyslipidemic state, plasminogen activator inhibitor-1 (PAI-1), which promotes a prothrombotic state, and high sensitivity-C-reactive protein (hs-CRP) and inflammatory cytokines, which promote a proinflammatory state (5). An increased waist circumference and/or waist: hip ratio, which reflects an excess of abdominal fat, correlates well with development of the metabolic syndrome and with cardiovascular risk (5)(7).

Clinical features have been proposed to facilitate diagnosis of the metabolic syndrome. The National Cholesterol Education Program (NCEP) proposed that the metabolic syndrome is present when any three of the following are found: 1) increased waist circumference (greater than 102 cm in men and 88 cm in women), 2) elevated fasting triglycerides (equal to or greater than 150 mg/dL), 3) reduced high density lipoprotein (HDL) cholesterol (less than 40 mg/dL in men and 50 mg/dL in women), 4) elevated blood pressure (equal to or greater than 130/85mm Hg) and 5) elevated fasting plasma glucose (equal to or greater than 110 mg/dL) (2)(5). The NCEP diagnostic criteria are relatively easy to implement in large clinical trials. Presence of the metabolic syndrome has been shown to increase the risk of cardiovascular disease in a number of studies in various populations (7)(8)(9)(10)(11)(12)(13).

Several studies have shown that patients with symptoms of the metabolic syndrome and additional cardiovascular risk factors, such as diabetes (14), smoking (15), or underlying coronary artery disease (16), are at even higher risk for atherothrombotic cardiovascular events than are those with the metabolic syndrome alone. One study (17) demonstrated that those with the metabolic syndrome who had an elevated CRP greater than 3.0 mg/L had an increased risk of cardiovascular events compared with those whose CRP was less than 3.0 mg/L. Another study (4) showed that the risk of coronary events increased as the number of metabolic syndrome factors increased. While the trials previously mentioned showed that the metabolic syndrome increased the risk of cardiovascular events even when the investigators controlled for other risk factors, a recent analysis of the Framingham Heart Study data showed that the addition of the specific components of the metabolic syndrome to their current scoring system did not improve risk prediction over the assessment based on currently used Framingham risk factors (18). This study

demonstrates the importance of multiple risk factors in determining cardiovascular event rate.

Current therapeutic recommendations for patients with the metabolic syndrome include weight reduction, recommended to be achieved by a combination of reduced caloric intake and increased exercise, and pharmacologic treatment of associated hypertension, diabetes, and dyslipidemia, if present and not responding to dietary measures (2). For those who smoke, smoking cessation is also emphasized (19). However, despite several years of publicity about the epidemic of obesity and the risks of a sedentary lifestyle, the prevalence of the metabolic syndrome is increasing (20). There is currently on the market no drug therapy specific for treating insulin resistance and its consequences, ie, symptoms of the metabolic syndrome.

4.2 Rationale for evaluating the beneficial effect of rimonabant on risk of cardiovascular events in patients with abdominal obesity and clustering risk factors

The endocannabinoid system (EC system) has recently been identified and characterized in animals and humans, and its role continues to be explored. The EC system is believed to play an important role in maintaining energy balance by helping to regulate food intake and energy storage. Increased activity of the EC system is associated with excessive food intake and fat accumulation in overweight and obese people. There is evidence of cannabinoid receptor expression in the periphery, in particular in adipocytes from mouse, rat, and human fat pads, supporting a role of endogenous cannabinoids in peripheral metabolic processes regulating energy storage. It is now realized that the adipose tissue functions as an endocrine organ, producing a variety of secreted factors, including leptin, adiponectin, tumor necrosis factor alpha, resistin, and plasminogen activator inhibitor-1. These so-called adipocytokines play important roles in metabolic homeostasis and, when their production is not properly regulated, they can contribute to metabolic disease, such as the metabolic syndrome and type 2 diabetes, and atherosclerosis. The role of the endocannabinoid system in regulating this endocrine function of adipocytes is being studied.

Rimonabant is the first potent, selective antagonist of the CB1 cannabinoid receptors, which, as noted above, are located in central and peripheral areas of the body and are associated with lipid and glucose metabolism. This compound blocks the pharmacological and behavioral effects of cannabinoid agonists in in vitro and in vivo studies. By selectively blocking CB1 receptors, rimonabant normalizes activity in the EC system, resulting in weight loss and improvements in cardiovascular risk factors. Notably, improvements in the metabolic complications associated with obesity, particularly abdominal obesity, are demonstrated, including improved insulin sensitivity, reduction in the occurrence of type 2 diabetes, the metabolic syndrome, and associated atherogenic dyslipidemia. Rimonabant has been shown to significantly reduce triglycerides and increase the HDL-cholesterol to low density lipoprotein (LDL) cholesterol ratio in an animal model. Rimonabant also increases adiponectin, an adipocytokine with anti-inflammatory and anti-atherogenic properties, demonstrating an effect on the peripheral CB1 receptors.

Rimonabant has recently been studied in several large clinical trials. The trials and their specific efficacy and safety results are summarized in the Clinical Investigator's Brochure.
Four double-blind, placebo-controlled Phase 3 studies were conducted to examine the effects of rimonabant on waist circumference, high serum triglycerides, low HDL-cholesterol and glucose control in patients with metabolic syndrome, and on weight management, type 2 diabetes, and obesity-related dyslipidemia. Each study, RIO-North America, RIO-Europe, RIO-Lipids, and RIO-Diabetes, had as its primary endpoint weight loss and weight maintenance at one year. Each study was conducted in overweight or obese patients with other cardiovascular risk factors. RIO-North America and RIO-Europe assessed prevention of weight regain, weight maintenance, and related metabolic risk factors over two years. RIO-Lipids, conducted in dyslipidemic obese patients, evaluated the effects of rimonabant on lipids and glucose tolerance. RIO-Diabetes, conducted in overweight and obese type 2 diabetics, evaluated the effects of rimonabant on hemoglobin A1c (HbA1c), fasting plasma glucose, and lipids. In each study a hypocaloric diet was prescribed and exercise was recommended. Over 6600 patients received rimonabant at either a 5 or 20 mg daily dose.
Statistically significant and clinically meaningful mean weight reductions from baseline to one year for rimonabant 20 mg versus placebo were demonstrated in these four large trials. Additionally, rimonabant 20 mg was effective in maintaining weight loss to two years in the RIO-North America and RIO-Europe trials.
In RIO-Diabetes, the group receiving rimonabant 20 mg for one year demonstrated statistically significant improvements in HbA1c and fasting plasma glucose compared with the placebo group. In addition to the improvement in glycemic parameters, there were significant improvements in lipid parameters and the metabolic syndrome in this diabetic population receiving rimonabant.
In the three clinical studies that included only nondiabetic patients, glucose and insulin homeostasis were assessed using fasting plasma glucose and a 2-hour oral glucose tolerance test (OGTT), the latter performed in RIO-Europe and RIO-Lipids. Patients with either an abnormal fasting glucose level at baseline or an abnormal OGTT represented over 28% of the population of the three studies. This group of pre-diabetic patients treated with rimonabant 20 mg experienced an improvement in glucose control as reflected by less insulin required to control fasting glucose, compared with a higher insulin requirement in patients receiving placebo. Likewise, significantly less insulin was needed to control the glucose load during the OGTT in patients receiving rimonabant 20 mg compared to the placebo group.
All four clinical trials included patients with obesity-related dyslipidemia (low HDL-cholesterol and/or high triglycerides, treated or untreated). In these studies rimonabant 20 mg showed consistent, statistically significant, and clinically meaningful effects on lipid profiles, reducing plasma triglycerides, increasing HDL-cholesterol, and decreasing the total cholesterol to HDL-cholesterol ratio. In patients with low HDL-cholesterol plasma levels at baseline, the increases in HDL-cholesterol from baseline to one year seen with rimonabant 20 mg were of greater magnitude than those seen in the overall population. Likewise, in patients with elevated triglycerides at baseline, decreases in triglycerides were of greater magnitude than in the overall population. The specific contribution of rimonabant versus weight loss itself to the increased HDL-cholesterol and decreased triglyceride levels observed in these studies was assessed by standard regression

methodology. Nearly 50% of the effect of rimonabant on HDL-cholesterol and triglycerides was independent of weight loss.
A subset of patients enrolled in RIO-North America, RIO-Europe, and RIO-Diabetes received concomitant therapy with HMG-COA reductase inhibitors. In this population with HDL-cholesterol levels in the lower range of normal, rimonabant significantly increased HDL-cholesterol levels and significantly decreased elevated baseline triglycerides, regardless of diet and concomitant lipid therapy.
In addition to the beneficial effects of rimonabant 20 mg on the lipid profile observed in the RIO-Lipids trial, effects on LDL particle size and adiponectin levels were measured in a subset of patients in this trial. Compared to placebo, the LDL particle size distribution shifted to larger, less dense and less atherogenic particles in patients treated with rimonabant 20 mg. There was also a significantly greater increase in plasma adiponectin levels at one year in those receiving rimonabant 20 mg compared to those on placebo.
In patients with the metabolic syndrome at baseline from all four studies, improvements in the risk parameters specified in the NCEP ATP III guidelines for the diagnosis of metabolic syndrome were seen. At one year, rimonabant 20 mg was effective in reducing waist circumference and triglycerides and increasing HDL-cholesterol. Fasting plasma glucose was significantly reduced in diabetics. Rimonabant 20 mg was effective in reducing the number of patients with metabolic syndrome regardless of which risk parameters led to this diagnosis. In both two-year clinical trials (RIO-North America and RIO-Europe), improvements in the risk parameters of the metabolic syndrome were maintained over the two years of treatment with rimonabant.
In all clinical trials of rimonabant, the safety profile and tolerability has been acceptable. No significant safety concerns have been raised in these trials.

In summary, use of rimonabant, at a 20 mg daily dose, has been associated with significant weight loss and a decrease in waist circumference compared to placebo in several clinical trials. Other effects seen in some of the trials include a significant increase in HDL-cholesterol and adiponectin, and decreases in triglycerides, in small, dense atherogenic LDL particles, and in C-reactive protein. Insulin sensitivity was improved with rimonabant treatment, in patients in whom this was studied. The proportion of obese patients with the metabolic syndrome, as diagnosed at study entry, was cut in half after one year of treatment with rimonabant. These effects were maintained over two years with continued drug treatment. Importantly, the metabolic effects of rimonabant could not be explained on the basis of weight loss alone. Thus, rimonabant demonstrated favorable effects on metabolic cardiovascular risk factors independent of weight loss.

4.3 Rationale for this trial design

Administration of 20 mg rimonabant over either one or two years has been shown to favorably modify, both directly and indirectly, most components of the metabolic syndrome that are associated with an increased risk of major cardiovascular events, as well as the presence of the metabolic syndrome itself. Thus, it is reasonable to examine whether use of rimonabant 20 mg, in patients with abdominal obesity who are at increased risk of a cardiovascular event, could be associated with a significant reduction in cardiovascular events. Patients with the metabolic syndrome alone generally have a

moderate risk of cardiovascular events, defined as a 10% to 20% risk of an event within the subsequent 10 years. Those with additional risk factors are considered to have a high risk, defined as greater than a 20% risk of an event within 10 years (2). In order to see the effects of 20 mg rimonabant therapy on this higher risk group, a large multiyear cardiovascular outcomes study is needed. For these reasons, it is planned to study rimonabant's ability to reduce the risk of a major cardiovascular event in patients with abdominal obesity who are at increased risk of such events in this large, multinational, multicenter randomized trial. Other medications that treat dyslipidemia, such as the HMG-COA reductase inhibitors, have demonstrated the ability to reduce major cardiovascular events, but in prior studies it has taken at least one year to demonstrate any effect. Thus, a long-term multiyear study is planned to demonstrate that rimonabant's favorable metabolic effects can reduce major cardiovascular events.

The population proposed for inclusion in the EFC5826 (CRESCENDO) study includes males and females aged 55 years or greater, with abdominal obesity and additional specified cardiovascular, including cerebrovascular, risk factors. The proposed primary efficacy endpoint is to evaluate the efficacy of rimonabant, compared to placebo, in reducing the occurrence of myocardial infarction, stroke, or cardiovascular death. Therefore, the population should be at increased risk for such events, based on published data and well-known cardiovascular risk factors. In this study, abdominal obesity is defined as per the NCEP guidelines for waist circumference (2). Abdominal obesity, as defined by waist circumference, is a recognized risk factor for cardiovascular events (7). Patients in this trial will be of older age, which increases their risk of an event (21). They will have additional risk factors, such as documented symptomatic cardiovascular disease, with evidence of coronary heart disease, cerebrovascular disease, peripheral arterial disease (21)(22), or type 2 diabetes mellitus, which is recognized as a coronary heart disease equivalent (23). If they do not have symptomatic cardiovascular disease or diabetes, they will have a combination of other risk factors that increase their risk of events. They may have the metabolic syndrome, as defined by NCEP guidelines (2)(5), with at least two of the following: elevated triglycerides, low HDL-cholesterol, mild elevation of fasting plasma glucose, and hypertension. Presence of the metabolic syndrome has been demonstrated to increase the risk of cardiovascular events, as documented above. In addition to the metabolic syndrome, they will have one other risk factor from among the following: asymptomatic cardiovascular disease [carotid artery disease, renal artery stenosis, or peripheral arterial disease (24)(25)(26)(27)(28)(29)], history of abdominal aortic aneurysm repair (30), advanced age of 65 years or older for males or 70 years or older for females (21), or elevated (greater than 3 mg/L) hs-CRP (17)(31)(32). Patients may qualify with age 55 or greater and four components of the metabolic syndrome, abdominal obesity plus three other risk factors. The risk for cardiovascular events increases as the number of components of the metabolic syndrome increases (4). Patients may qualify for enrollment without either symptomatic cardiovascular disease or the metabolic syndrome, but in those cases all will have abdominal obesity and older age, and will have at least two other risk factors from among the following: asymptomatic cardiovascular disease, abdominal aortic aneurysm repair, advanced age, or elevated hs-CRP.

While presence of the metabolic syndrome alone, without overt diabetes, increases the risk of cardiovascular events to a mild to moderate degree, the population included in this trial

will have a greater degree of cardiovascular risk. Based on a prior trial in a similar high risk population, the estimated cardiovascular event rate in the proposed population is calculated to be 3% per year. Such a cardiovascular risk warrants pharmacologic therapy, according to published guidelines (19). Thus it is reasonable to study the effect of rimonabant therapy with 20 mg daily in this high risk population, with multiple risk factors that have been shown in prior trials to be improved by rimonabant therapy.

5. STUDY OBJECTIVES

5.1 Primary Objective

To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of myocardial infarction, stroke, or cardiovascular death (as defined in Section 9.1.2.1.3) in patients with abdominal obesity at increased risk for such events.

5.2 Secondary Objective

To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of myocardial infarction, stroke, cardiovascular death (as defined in Section 9.1.2.1.3), or hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure), in patients with abdominal obesity at increased risk for such events.

5.3 Other Objectives

To demonstrate the effect of rimonabant versus placebo on all-cause mortality.

To assess the safety of rimonabant in the study population over the duration of the study.

6. STUDY DESIGN

6.1 Description of the protocol

The present study is designed as a multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm parallel-group trial.

6.2 Duration of study participation

The estimated study duration that served as the assumption for sample size calculations is 50 months. All randomized patients will be followed to a common study end date, which is estimated to occur when the last randomized patient has been followed for 33 months, based on a 17-month recruitment period.

6.3 Interim analysis

There will be no interim analysis during this study.

6.4 Study committees

The Cleveland Clinic Cardiovascular Coordinating Center (C5) group will be in charge of the logistical coordination of the different study committees. Distinct responsibilities of C5 and the study Sponsor are provided in Appendix 1.

Executive Committee

The Executive Committee of the study is composed of Investigator/Academic Members from participating countries and Sponsor Representatives. This Committee, led by its Chairman, Professor Eric J. Topol, MD, will provide scientific and strategic direction for the trial and will have overall responsibility for its execution. Detailed responsibilities and membership for this committee are provided in Appendix 2.

Operations Committee

The Operations Committee is responsible for ensuring that study execution and management are of the highest quality. This Committee will be composed of the Chairman and co-Chairmen of the Executive Committee, as well as the International Principal Investigator and nonvoting Sponsor Representatives. It will determine its own guidelines and approve the criteria and guidelines of the other Committees prior to commencement of the study. The Operations Committee will convene regularly (at least every 3 months) to discuss and report on the progress of the study. Detailed responsibilities and membership for this Committee are provided in Appendix 3.

Clinical Events Committee (CEC)

The CEC is composed of multidisciplinary academic members. This Committee, coordinated by C5, will be responsible for validating and classifying, in a blinded fashion, all the primary efficacy outcome events (myocardial infarction, stroke, and cardiovascular death) reported by the Investigators. Detailed responsibilities and membership for this Committee are provided in Appendix 4.

Data Monitoring Committee

The Data Monitoring Committee (DMC) is composed of Academic Members who are not otherwise participating in the trial. This Committee, led by its Chairman, Dr. Robert Frye, will be responsible for the monitoring of patient safety, and it will be supported by an external DMC-associated statistician. Detailed responsibilities and membership for this Committee are provided in Appendix 5.

The DMC can request any analysis during the course of the study, on either a blinded or unblinded basis.

The independent DMC-associated statistician will perform the planned analyses as well as the other analyses requested by the DMC, independently from the Sponsor. This

independent statistician will be provided with the randomization code list, as well as with regular database transfers. He/she will prepare pro-forma tables, listings, and a report for submission to the DMC. Safety data will include serious adverse events (SAEs), outcome events, local laboratory values, plus other adverse events (AEs) as requested by the DMC. Demography, treatment and trial status data will be presented as requested by the DMC. The report will be based on current data, whether clean or not, and whether adjudicated or not. Although efficacy data will be provided, DMC review of these data does not constitute a formal interim analysis of efficacy, and any analyses of these data will not, in and of themselves, be used for stopping the trial.

National Leadership

In most countries, a National Coordinator will be named. The National Coordinators will be given the following responsibilities:

- Assist the Sponsor in identifying clinical centers, whenever necessary,
- Support the Sponsor for local Investigators' meetings,
- Maintain close contacts with clinical centers,
- Provide scientific and operational support locally, in liaison with the Sponsor and C5.

7. SELECTION OF PATIENTS

7.1 Number of patients planned

Based upon the anticipated event rates, premature treatment discontinuation and expected relative efficacy, approximately 17,000 patients will be enrolled in the study, with approximately 8,500 patients in each arm.

7.2 Inclusion criteria

1. Written informed consent obtained
2. Men and women aged 55 or older, **AND**
3. Presence of abdominal obesity, with a waist circumference greater than 102 cm (40 inches) for males and greater than 88 cm (35 inches) for females on three successive measurements at the baseline visit, **AND**
4. Presence of at least one coronary heart disease (CHD) risk equivalent **OR** two major cardiovascular risk factors

Coronary heart disease risk equivalents:

a) Recent (within the past 3 years) myocardial infarction (MI) (**two of the following three criteria** must be satisfied):
   - Characteristic ischemic chest pain or pain in associated referral areas or anginal equivalent symptoms,

- Elevation of CK (at least twice the upper limit of normal values for that laboratory) and/or CK-MB (at least twice the upper limit of normal values for the laboratory) and/or troponin T or I (at least above the upper limit of normal for the laboratory),
- Development of Q waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1.

b) Stable angina with documented multivessel coronary disease (defined as greater than 50% stenosis in at least two epicardial coronary arteries at angiography), **and/or** history of multivessel percutaneous coronary intervention (PCI) or multivessel coronary artery bypass graft (CABG)
TOGETHER WITH at least one of the three following criteria:
   - Current exercise-induced angina pectoris
   - Positive ECG stress test (ST depression greater than 2 mm with normal baseline ST segments)
   - Reversible defect by myocardial perfusion imaging or stress-induced wall motion abnormality on stress echocardiography test

c) Recent (within the past 3 years) cerebrovascular disease, as evidenced by an ischemic cerebrovascular episode (**all criteria** must be satisfied):
   - A focal neurological deficit
   - Without evidence of a cardio-embolic origin
   - Without evidence of non-vascular origin on CT or MRI scan

   CT or MRI must have been performed to document whether there is a lesion and to rule-out non-ischemic neurological disease.

d) Documented symptomatic peripheral arterial disease (PAD) (**one of the following primary criteria** must be satisfied):
   - current intermittent claudication (WHO criteria, eg, leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin **TOGETHER WITH** ankle-brachial index equal to or less than 0.85 in either leg at rest, OR
   - history of intermittent claudication (WHO criteria as above) **TOGETHER WITH** either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease,

e) Type 2 diabetes mellitus (fasting plasma glucose equal to or greater than 126 mg/dL [7.0 mmol/L] on two or more occasions)

Major cardiovascular risk factors:

f) Metabolic syndrome, **as diagnosed by the presence of at least 2 of the following risk factors (if 3 of the risk factors listed below are fulfilled, this is equivalent to two major risk factors and the patient is eligible**):
   - Fasting triglyceride level equal to or greater than 150 mg/dL (1.69 mmol/L)
   - HDL-cholesterol less than 40 mg/dL (1.03 mmol/L) for males or less than 50 mg/dL (1.28 mmol/L) for females
   - Fasting plasma glucose equal to or greater than 110 mg/dL (6.1 mmol/L)
   - Blood pressure equal to or greater than 130 mm Hg systolic and/or 85 mm Hg diastolic at baseline visit

g) Cerebrovascular disease (**at least one of the following three criteria** must be satisfied):
   - Asymptomatic disease of the carotid, intracranial, and/or vertebral arteries, with greater than 50% stenosis
   - At least one carotid plaque on ultrasonography, defined as a distinct area with an intima-media thickness (IMT) exceeding twice that of neighboring sites, OR
   - Prior cerebrovascular revascularization procedure

h) Renal artery disease, with greater than 60% stenosis on MR angiography, CT angiography, or angiography, or prior revascularization procedure
i) Previous history of abdominal aortic aneurysm repair
j) Asymptomatic ankle-brachial index less than 0.85
k) Elevated hs-CRP greater than 3 mg/L
l) Males 65 years or older or females 70 years or older

7.3 Exclusion criteria

7.3.1 Related to general patient characteristics

1. Obesity due to known endocrine disorder, such as hypothyroidism, or hypopituitary or other endocrine disease
2. Pregnant or breast-feeding women, or women planning to become pregnant or to breast feed[12]
3. Very low-calorie diet (1200 calories a day or less) or surgical procedure for weight loss (eg, stomach stapling, bypass, etc) within 6 months prior to baseline visit
4. Presence of any severe medical condition or advanced age such that the patient is not expected to survive for the planned study follow-up period

[12] Women of childbearing potential must have a negative urine beta-human chorionic gonadotropin (β-HCG) pregnancy test at the baseline visit and must commit to using an acceptable form of contraception during the entire study period, up to three months after last study drug intake. Women using oral contraception must also have done so for 3 months prior to randomization. To be considered not of childbearing potential, women must be post-menopausal for at least 1 year or surgically sterile.

5. Presence of any severe medical or psychological condition that, in the opinion of the Investigator, would compromise the patient's safe participation
6. Presence of any condition (medical, psychological, social, or geographical), actual or anticipated, that the Investigator feels would restrict or limit the patient's successful participation for the duration of the study
7. Receipt of any investigational treatment (drug or device) within 30 days prior to baseline visit
8. Previous participation in a rimonabant study
9. Known allergy to rimonabant or excipients

7.3.2 Related to cardiovascular condition

10. Clinically significant cardiovascular disease that, in the opinion of the investigator, is likely to require intervention (PCI, CABG, valve repair/replacement, heart transplantation, PTA, peripheral bypass surgery, endarterectomy, etc) within the next one month after randomization

8. TREATMENTS

8.1 Investigational Product

- Presentation:
  - White-opaque tablets, for oral administration, containing either 20 mg of active rimonabant or matching placebo, and excipients including maize starch, lactose monohydrate, povidone, croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, and magnesium stearate.

- Modalities of administration:
  - 1 tablet every day during treatment phase (ie, up to Study End Date)
  - Tablet must be administered orally in the morning before breakfast.

- Dosage according to study group:
  - During treatment period (from day 1 (post-randomization) to Study End Date
    - Group 1 (rimonabant 20 mg): once daily (OD) administration of 1 tablet containing 20 mg of active rimonabant
    - Group 2 (placebo): once daily administration of 1 rimonabant placebo tablet

8.2 Description of blinding methods

- The two types of tablets developed (20 mg rimonabant and placebo rimonabant) are indistinguishable (identical in size, shape, color, and appearance), and are packaged in identical wallet cards.
- No biological test that could potentially unblind the treatment is planned in this study.

- Investigators do not have access to the randomization (treatment) code except in case of a serious adverse event. In this case, the code may be broken only in exceptional circumstances when knowledge of the study medication is essential for treating the patient.

8.3 Method of assigning patients to treatment group

The Interactive Voice Response System (IVRS) center will allocate treatment based on a pre-specified randomization list, generated by the IVRS provider, using study center as stratification parameter. A list of treatment kit numbers for each treatment group is generated centrally by sanofi-aventis and the treatment kits are prepared in accordance with this list. Numbers will not be reused regardless of the status of the use of the corresponding study drug.

After the patient signs the informed consent, and after eligibility is documented based on inclusion/exclusion criteria, the Investigator will call the IVRS center to receive the number for that treatment kit and the subject number to be allocated to the patient. Patients will be considered randomized as soon as the first allocation of treatment kit number is given as documented by the IVRS center.

All patients who are allocated a treatment kit number (ie, randomized) by the IVRS are irrevocably in the study, whether or not they are subsequently found to be eligible or actually receive the allocated treatment, and they should be followed until the End of Study visit or death, whichever comes first.
The first study drug intake should take place as soon as possible after randomization (on the same day), under medical supervision. If patients temporarily discontinue study medication, they should resume taking it as soon as possible.

8.4 Packaging and labeling

Rimonabant tablets and matching placebo will be packaged in identical primary wallet cards. Each wallet card will contain 36 tablets and will be labeled with a treatment number (in addition to protocol number, expiry date, packaging number, and all the necessary regulatory statements required for each country participating in the study). Seven (7) wallets will be placed in a kit box, which will contain a six (6)-month supply of treatment plus an additional month (252 tablets total). Four kit boxes will be placed in a partial shipment unit (PSU) box with a set of decoding envelopes, for the purpose of unblinding the treatment. Each kit box will bear a unique treatment number corresponding to the treatment number on each of the wallet cards inside. All kit box labels will be multilingual and will meet regulatory requirements necessary for each participating country.
During the course of the 33 to 50 month treatment period, patient drug re-supply will be requested at each 6-monthly visit (6-month, 12-month, 18-month, etc), and a new treatment kit number will thus be assigned by the IVRS at each of these time points. The treatment type, rimonabant or placebo, will not change.

A patient who completes the protocol as defined will have no less than six (6) unique treatment kit numbers, one from randomization and one from each 6-month re-supply visit.

8.5 Storage conditions

All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual.

8.6 Access to the randomization code during the study

The Investigator (or Pharmacist) will be supplied with one decoding envelope for each treatment kit number.
It is the responsibility of the Investigator (or Pharmacist) to ensure that these decoding envelopes are safely stored, but are readily available to the relevant staff.
Additional unblinding materials (envelopes) will be available and are to be kept in a safe place at CRU level (or subcontractor, if any) throughout the clinical trial.
The Sponsor will retrieve all envelopes, whether opened or sealed, on study completion.

In case of a Serious Adverse Event, the code should be broken only in exceptional circumstances when knowledge of the Investigational Product is essential for treating the patient.
In case the physician at the investigational site believes unblinding is needed, he/she must first contact the Medical Advisor located at C5 for further direction. All calls will be documented as appropriate to include date and time of the call, name of the C5 Medical Advisor, name, qualification, and address of the physician contacting C5, patient ID, documentation of the request, and decision for unblinding or not.
If possible, a contact should be initiated with the Monitoring Team before unblinding.
In case the decision to unblind is made, the Investigator must document it with the date, time of day, and reason for unblinding, and report this information in the appropriate page of the CRF and source document. In addition, the IVRS (24-hour unblinding service) must be notified of this decision.

Note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the Investigational Product. The Investigator should not divulge medication detail to any C5 staff member, to the Sponsor's representative, or to any Study Committee members until database closure. Furthermore, when completing forms (eg, AE, SAE), the study treatment should not be disclosed on the forms. The unblinding envelopes will be sealed again and stored at the site level until the end of the study (envelopes opened by the CRU or a subcontractor must also be sealed again).

8.7 Responsibilities

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (IP) will be responsible for ensuring that the IP used in the study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All IP shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IP (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply IP to a third party, allow IP to be used other than as directed by this Clinical Trial Protocol, or dispose of IP in any other manner.

8.8 Retrieval and/or destruction of Investigational Product

All partially used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy unused IP unless the Sponsor provides written authorization to the contrary.

A potential defect in the quality of IP may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IP and eliminate potential hazards.

8.9 Concomitant treatment

8.9.1 Prohibited concomitant treatment

- Anti-obesity drugs (eg, sibutramine, orlistat, phentermine, amphetamines, open-label cannabinoid receptor antagonists, or other drugs or herbal or over-the-counter medications for weight reduction)

- Thyroid preparations other than thyroxin replacement treatment.

8.9.2 Permitted concomitant treatment

Any drugs other than those listed above are allowed, and should be administered, as necessary for the treatment of the patient, when possible with a stable dose, at the discretion of the Investigator. Treatment for dyslipidemia, hypertension, and/or diabetes should be initiated as soon as the need for treatment is identified, in accordance with treatment guidelines provided and standard of care, and should be adjusted as necessary to treat the patient’s condition(s). All treatment with these drugs should be recorded on the appropriate CRF.

8.10 Treatment compliance

Compliance is assessed by counting the number of returned tablets in each wallet card at each visit. The Investigator (or delegate) must complete the appropriate pages of the treatment log form and of the CRF. A discontinuation is defined as a period with a least five consecutive days without study drug intake.
The monitor supervising the study will verify the data by comparing the recorded data with the investigational product retrieved.

9. ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 Efficacy

9.1.1 Efficacy criteria

9.1.1.1 Primary criterion

The first occurrence of any component of the following cluster, as adjudicated by the Clinical Events Committee:

- Any MI (nonfatal or fatal[13])
- Any stroke (nonfatal or fatal[13])
- Cardiovascular death

9.1.1.2 Secondary criterion

The first occurrence of any component of the following cluster:

- Any MI (nonfatal or fatal[13])
- Any stroke (nonfatal or fatal[13])
- Cardiovascular death, and
- Hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure)

9.1.1.3 Other criteria

All-cause mortality

[13] The diagnosis of fatal MI or fatal stroke is based upon:

- either death occurring within 28 days of the onset of the acute MI or stroke, in the absence of other clear cause,
- or death occurring more than 28 days after the onset of the acute MI or stroke, if that is the best clinical judgment and/or the CEC judges MI or stroke to be the cause of death, as appropriate,
- or autopsy confirmation of an acute MI or stroke as cause of death.

The following events taken separately:

- Myocardial infarction (nonfatal or fatal[13]).
- Any stroke (nonfatal or fatal[13]/ischemic, hemorrhagic or of uncertain type).
- Cardiovascular death
- Hospitalization for unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure.

9.1.2 Clinical assessment methods

9.1.2.1 Definitions of components of the primary efficacy endpoint:

9.1.2.1.1 Myocardial infarction (MI)

Based on American College of Cardiology (ACC) Definitions for Measuring Outcomes (33), three main situations will be considered:

1. Patient who did not undergo recent cardiac intervention (within prior 24 hours):
   At least one of the following must be present (biomarker assay must be performed):
   a) CK-MB elevation (>2xULN in one sample or >ULN in two samples)
   b) Troponin elevation (>ULN in one sample)
   c) CK elevation (in absence of a and b, CK >2xULN)

AND

At least one of the following (ECG must be performed and documentation should be provided to the Clinical Events Committee):

- Ischemic symptoms within last 24 hours
- ST depression of at least 0.1 mV or T wave inversion
- LBBB (new or old) or paced rhythm that obscures assessment of ST
- ST elevation (new ST elevation in at least two contiguous leads ≥0.2 mV in V1, V2, or V3 or ≥0.1 mV in other leads)
- New tall R wave with R/S ≥1 in V1 and R/S ≥1.5 in V2
- New Q waves ≥40 ms in two contiguous leads

2. Patient who underwent recent PCI/CABG (within prior 24 hours):
   a. Percutaneous coronary intervention (PCI): CK-MB ≥3xULN (no ECG changes or symptoms required)
   b. Coronary artery bypass graft (CABG): either CK-MB ≥5xULN and new Q-waves, as defined above, or CK-MB ≥10xULN (with or without Q-waves)

3. If new Q-waves ≥40 ms in two contiguous leads occur in a diabetic patient, an MI diagnosis will be established even in the absence of ischemic symptoms and enzyme elevations.

MIs will be subsequently categorized as Q-wave MI or non Q-wave MI.

All appropriate supportive documentation should be provided to the Clinical Events Committee (see Appendix 4).

9.1.2.1.2 Stroke

Defined as an acute neurological vascular event with focal signs lasting more than 24 hours, with or without evidence of primary intracranial hemorrhage (PICH). Strokes will be further categorized as ischemic, hemorrhagic, or uncertain type.

If a previous deficit has worsened, it must have lasted more than one week, or more than 24 hours if accompanied by an appropriate new CT or MRI finding.

CT scan or MRI should be performed and should be provided in addition to other appropriate supportive documentation (see Appendix 4) to the CEC to allow further classification.

9.1.2.1.3 Cardiovascular death (CVD)

Defined as any death with a clear cardiac or vascular cause or unknown cause (including sudden death, unobserved and unanticipated death and other death not definitely attributed to a non-vascular cause). Only death due to a documented non-cardiovascular cause will be classified as non-cardiovascular. Death due to hemorrhage, other than PICH, and to pulmonary embolism will not be considered as a cardiovascular death.

Supportive documentation should be provided to the Clinical Events Committee for classification of cause of death (see Appendix 4).

9.1.2.2 Definitions of secondary efficacy endpoints:

9.1.2.2.1 Hospitalization

Defined as an overnight hospital stay, except for TIA, where treatment in an Emergency Department without hospital admission is acceptable, provided that the diagnosis of TIA is confirmed.

9.1.2.2.2 Transient ischemic attack (TIA)

Defined as a focal ischemic neurological deficit (cerebral or retinal), considered to be of ischemic origin, with a neurological deficit persisting less than 24 hours. As for stroke, CT scan or MRI should be performed to confirm the ischemic nature of the event.

9.1.2.2.3 Unstable angina (UA)

Defined as the onset of characteristic ischemic chest pain in the precordium or associated referral areas (occurring at rest or with minimal exercise, lasting longer than 5 minutes or requiring sublingual nitroglycerin for the relief of the pain), documented by ECG changes compatible with ischemia [e.g. ST depression (at least 1 mm in two contiguous leads), T-

wave inversion (at least 2 mm in two contiguous leads), or hyperacute peaked T waves, or new normalization of T waves], in the absence of fulfillment of the non-fatal MI definition.

9.1.2.2.4 Urgent revascularization procedure

Defined as any of the following procedures:

- Coronary revascularization: PCI (includes PTCA, coronary stenting, and others such as brachytherapy, atherectomy, laser, and rotational ablation) or CABG;
- Cerebrovascular revascularization: carotid endarterectomy, carotid percutaneous transluminal angioplasty (PTA with or without stent);
- Peripheral revascularization: peripheral arterial bypass surgery, PTA, or any therapeutic intervention for critical leg ischemia (including thrombolysis), or aortic aneurysm repair;

performed in an expedited fashion for worsening or unstable symptoms resulting in hospitalization.

9.1.2.2.5 Cardiac rhythm disorder

Defined as any abnormal cardiac rhythm, such as atrial fibrillation or ventricular arrhythmias and including any conduction abnormality, that is documented by ECG or Holter monitoring and requires an overnight hospital stay, prolongs hospitalization, or requires cardioversion or device implantation.

9.1.2.2.6 Congestive heart failure

Defined as inadequate cardiac output, as manifested by symptoms, such as dyspnea and/or orthopnea, and objective signs, such as peripheral edema, rales, jugular venous distension, arterial oxygen desaturation, and/or pulmonary edema on chest X-ray, found to be of cardiac cause.

9.1.2.2.7 Syncope

Defined as loss of consciousness that requires hospitalization for diagnosis and/or treatment.

9.1.2.3 Definition of other efficacy endpoint

9.1.2.3.1 Non-cardiovascular death (non-CVD)

Defined as any death with documented non-cardiovascular cause.

9.2 Safety

Safety evaluation will rely on capturing all AEs reported (including neurological and psychiatric AEs based on clinically relevant results of scripted questions asked at each follow-up visit and phone call and on physical examination findings), on vital signs

(supine heart rate and blood pressure) obtained at one, three and six month visits, then at every 6-month visit and at the final visit, and on physical examination and hematology (Hb, Ht, WBC-diff, platelets), and biochemistry (ALT, AST, ALP, creatinine) values obtained at 6-month visits and at the final visit.

10. PATIENT SAFETY

10.1 Adverse Events monitoring

Definitions:

An adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or asymptomatic ALT increase greater than 10x ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

Adverse Events

All Adverse Events regardless of seriousness or relationship to Investigational Product, including those from the first visit planned in the Clinical Trial Protocol/signature of the informed consent form, are to be recorded on the corresponding page(s) included in the

Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the Investigational Product.

Lab, vital signs, or ECG abnormalities are to be recorded as adverse events only if they are medically relevant: symptomatic, require corrective treatment, lead to study drug discontinuation and/or fulfill a seriousness criterion.

Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

- SEND (within 1 working day, by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol, or to a designated Safety fax number provided by the Monitoring Team, as well as to the Central Database number;

- ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly documented on all copies of source documents provided to the Sponsor. For laboratory results, include the laboratory normal ranges;

- Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week. The treatment code will be unblinded for reporting of Serious Adverse Events that are unexpected and reasonably associated with the use of the Investigational Product.

Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, including referral to a specialist if indicated. Notably he/she should follow up the outcome of any adverse events (clinical signs, laboratory values or other, etc) until the return to normal or stabilization of the patient's condition;
- In the case of any serious adverse event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This implies that follow-up may continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In case of any serious adverse event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered by him/her to be caused by the Investigational Product with a reasonable possibility, this should be reported to the Monitoring Team.

10.2 Pregnancy

In case of pregnancy, Investigational Product should be discontinued and the Sponsor informed. Follow-up of the pregnancy will be mandatory until the outcome is available.

10.3 Waiver

Expected cardiovascular efficacy endpoints specified in this trial (primary and secondary efficacy criteria) will not be considered as AEs and will not be subject to expedited regulatory reporting. They will be reported on specific outcome event forms, which should be sent within one (1) working day, by FAX, to the Central Database number.

11. HANDLING OF PATIENT WITHDRAWAL

11.1 List of withdrawal criteria

Occurrence of an outcome event according to the judgment of the Investigator must not be considered as a reason for study drug discontinuation.

Depending on the Investigator's judgment, permanent study drug discontinuation is only clearly justified for an adverse event, when qualifying condition is not present, or when a patient demands to withdraw from study drug treatment, and in such cases the appropriate follow-up until the study end date should still be continued.

Although patients may withdraw from the study drug at any time and for any reason, (or may be withdrawn at the Investigator's decision), patient withdrawal should be avoided as much as possible. If this occurs, every attempt should be made to restart study drug if medically appropriate, whatever the duration of discontinuation. Since the hypothesis being tested in this study is that rimonabant has beneficial cardiovascular effects not necessarily dependent on weight loss, patients should be encouraged to remain on treatment independently of observed weight loss.
The reason for study drug discontinuation will be recorded on the CRF. In any case, appropriate follow-up for efficacy and safety endpoints should be continued.

11.2 Follow-up procedures after withdrawal

Patients who prematurely discontinue study drug are not to be replaced.
All randomized patients must be followed up according to the study flowchart until study end date or death, regardless of whether they discontinued study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.
In case of study drug discontinuation (temporary or permanent) due to an adverse event, such patients will be closely monitored until the resolution or stabilization of this adverse event. This may mean that follow-up will continue after the patients have completed the study follow-up. Although data on that adverse event will continue to be captured, even

beyond the last visit, for new efficacy or safety events, only those that occur up through the last visit should be recorded.

In case of written withdrawal of consent (WOC) for follow-up visits, and unless otherwise stated by the patient in the informed consent form, Investigators will be encouraged to get information from the general practitioner, any other physician, or other medical-care provider, in order to follow the medical status of the patients (especially when they withdraw their consent after having experienced an AE/SAE or an efficacy endpoint). Investigators will also be expected to try as much as possible to re-contact those patients at the end of the trial, in order to obtain at least their vital status (dead or alive), as well as their stroke or MI status if possible, and thus avoid lost to follow-up for the efficacy assessment.

For patients considered lost to follow-up, the CRF must be completed up to the last visit performed.

11.3 Consequence

If the drug is stopped prematurely, every attempt should be made to restart it if medically appropriate, whatever the duration of discontinuation.
If the patient withdraws his/her consent for study participation, although in such circumstances he/she may not be obliged to comply with all the protocol visits and phone calls, the Investigators, the study nurses and any other study coordinators are requested to try to obtain as much as possible, the vital status of the patient (dead or alive at a minimum, preferably also stroke or MI status) at study end date. This will be clearly stated in the informed consent form.

Any direct communication with the general practitioner, any other physician or other medical-care provider can be helpful for following the medical status of the patient. This is particularly important if the patient withdraws his consent after experiencing an AE/SAE or an efficacy endpoint since for safety and Regulatory purposes, it is necessary to obtain some information regarding worsening or resolution of the event (especially if this event is considered as to be related to the Investigational Product).

In addition to the need for safety assessment, it is also important to avoid any lost to follow-up patients for the efficacy assessment and meaningful analysis of the study.

12. STUDY PROCEDURES

12.1 Visit schedule

See Section 1 flowchart at the beginning of the protocol.

12.1.1 Pre-screening procedures

Study subjects will be recruited from among participating hospitals, clinics, and diagnostic centers, under the responsibility of a participating Investigator.
Prior to initiation of the recruitment phase, participating Investigators will identify a pool of potential study subjects. Each of these centers will identify potentially eligible patients in advance, by either reviewing past medical records and diagnoses, admissions to coronary care units, admissions to stroke centers, logs of invasive and noninvasive laboratories and relevant surgical procedures, screening in diabetic clinics, referral from other physicians, or other sources of recruitment, to identify those aged 55 or older with increased waist circumference and other risk factors for atherosclerotic cardiovascular or cerebrovascular disease.

12.1.2 Baseline visit

The patient will receive complete information about the study both orally and in writing. Written informed consent must be obtained from the patient prior to any study-specific procedures and prior to randomization.
Compliance with inclusion criteria (listed in Section 7.2) and exclusion criteria (listed in Section 7.3) will be checked on the basis of information collected, and recorded in the CRF.
Key baseline patient characteristics obtained at the randomization visit will be recorded in the CRF, including demographics, vital signs, height, weight, waist circumference, relevant past medical and surgical history, including neurological and psychiatric history, and abnormalities noted on physical exam, including neurological exam.
Medical history, physical examination, laboratory, or instrumental results confirming inclusion and absence of exclusion criteria will be maintained in the patient's file.

12.2 Inclusion procedures

Once all inclusion/exclusion criteria are fulfilled, the patient becomes eligible for randomization and inclusion into the treatment period.
Treatment allocation will be performed as stated above (Section 8.3).
Study medication will be delivered as stated in Section 8.4.
Patients will be counseled to follow a mild hypocaloric diet, to increase their exercise level, and to stop smoking, if they are smokers.

12.3 Description by type of visit

- Baseline visit:
  - informed consent completed and signed
  - check of inclusion and exclusion criteria
  - demographic data
  - medical/surgical history, including neurological and psychiatric history (scripted questions)
  - current medications
  - smoking status

- supine blood pressure and heart rate
- physical exam, including detailed neurological exam
- body weight
- height measurement
- waist circumference
- 12-lead ECG
- hematology (Hb, Ht, WBC-diff, platelets)
- biochemistry (ALT, AST, ALP, creatinine)
- urinary pregnancy test (for women of childbearing potential)
- counseling on diet, exercise, and, if appropriate, smoking cessation
- call to the IVRS for allocation of a randomized treatment kit number
- delivery of the corresponding pack of study drug (containing the appropriate amount to allow daily administration until at least the next planned 6 month Treatment visit)
- first intake of study drug (under medical supervision)

- 1-month Treatment visit (Day 30 ± 7 days)
  - recording of all primary or secondary efficacy endpoints, if any
  - recording of AEs (including neurological and psychiatric AEs), if any
  - supine heart rate and blood pressure
  - check of study drug compliance
  - recording of concomitant medications

- 3-month Treatment visit (Day 90±14 days)
  - recording of all primary and secondary efficacy endpoints, if any
  - recording of AEs (including neurological and psychiatric AEs), if any
  - supine heart rate and blood pressure
  - check of study drug compliance
  - recording of concomitant medications

- 6-month Treatment visit (Day 180±14 days) and subsequent 6 month visits (every 180±14 days)
  - recording of all primary and secondary efficacy endpoints, if any
  - recording of AEs (including neurological and psychiatric AEs), if any
  - check of study drug compliance
  - recording of concomitant medications
  - body weight
  - waist circumference
  - supine heart rate and blood pressure
  - physical exam
  - 12-lead ECG, at penultimate (next to last) visit. The presence of abnormalities, including new pathological (as defined in Section 9.1.2.1.1) Q waves, will be recorded. If a silent MI is diagnosed in a diabetic patient, an MI outcome form will be completed.
  - hematology (Hb, Ht, WBC-diff, platelets)
  - biochemistry (ALT, AST, ALP, creatinine)

  - call to IVRS center for allocation of the second or subsequent treatment kit number
  - delivery of the pack of study drug corresponding to treatment kit number, containing the appropriate amount to allow daily administration until at least the next planned 6-month Treatment visit

- Final (end-of-study) visit may occur up to 30 days after but never before the study end date;
  - recording of all primary and secondary efficacy endpoints
  - recording of AEs (including neurological and psychiatric AEs)
  - check of study drug compliance
  - recording of concomitant medications
  - supine blood pressure and heart rate
  - physical exam
  - body weight
  - waist circumference
  - hematology (Hb, Ht, WBC-diff, platelets)
  - biochemistry (ALT, AST, ALP, creatinine)

Every attempt should be made to complete the follow-up visits during the defined window periods.
A final follow-up visit is required for all patients. In the rare cases a final follow-up visit cannot occur within the 30-day timeframe following study end date, any attempt to contact should be recorded on a special contact form, until/unless appropriate information is obtained which will allow completion of final follow-up visit CRF, even after the anticipated timeframe.

After the 6-Month Visit and between subsequent scheduled 6-monthly visits, the Investigator or his designee should contact the patient by phone, ie, at 9 months, 15 months, 21 months and every 6 months thereafter. These regular phone contacts will permit earlier collection of data related to efficacy or safety (including neurological and psychiatric AEs, when clinically relevant observations are made using the scripted questions) and will encourage patient compliance, but they do not aim at making any medical diagnosis by phone. In case an event is identified during a phone call, a subsequent office visit may be required in order to allow appropriate documentation of the efficacy or the safety event. **There is no strict timing for the phone calls. In any case, it is better to call the patient after a delay, than to not call him at all (even in this case, the phone call record page of the CRF should be completed).**

The patient visit schedules will be given by the IVRS as soon as the patient is randomized, so as the Investigator can plan in advance all the necessary appointments with the patient.

12.4 Definition of source data

All the data collected in the CRF come from source documents that are part of the patient dossier. Copies of some of those source documents will be collected after anonymization,

in order to support documentation of outcome events eligible for validation by the Clinical Events Committee, ie:

- for any of those events: a copy of the Hospital Discharge Summary and a clinical description of the event by the Investigator
- for any death: a copy of the death certificate (if applicable and available), autopsy report (if available), 12-lead ECGs (all, including baseline), other relevant reports, and witness description of the death
- for any sudden death: a copy of recent Holter reports (if available) and cardiology notes
- for MI: a copy of the ECG tracings selected from serial ECG and documenting Q-wave MI or non Q-wave MI, biochemical reports (cardiac markers + laboratory reference values) selected from serial tests (eg, peak values) relevant to the diagnosis of MI or re-MI, autopsy report (if available) or other relevant reports (coronary angiography, echocardiography)
- for stroke: CT-scan / MRI report and copy of the films, autopsy report (if available) or other relevant reports (angiography, Doppler sonography…).

13. STATISTICAL CONSIDERATIONS

13.1 Statistical and analytical plans

The material of this section is the basis for the Statistical Analysis Plan of this study. This plan may be revised during the study to accommodate Clinical Trial Protocol Amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to data lock.

13.2 Determination of sample size

Based on the targeted population for the study, 3% is considered a reasonable assumption for the yearly event rate in the placebo group. Assuming recruitment over a 17 month period, and a total study duration of 50 months, 8,500 patients per group (total 17,000) will give a power of 90% (two-sided test, at the 5% significance level) to the trial to show an overall 15% risk reduction (or equivalently no effect the first year, followed by a 25% risk reduction in subsequent years). This corresponds to approximately 1,600 events.

These computations allow for a 10% annual rate of treatment discontinuation.

13.3 Study patient description

13.3.1 Disposition of patients

The number of randomized patients will be summarized by country and center using counts and percentages.
The number of patients either completing or permanently discontinuing the study drug period will be summarized using counts and percentages.

13.3.2 Clinical Trial Protocol deviations

All the following deviations will be summarized on the all randomized patient population:

- Inclusion or exclusion criteria not satisfied.
- Deviations related to the study drug administration
- Not permitted concomitant medications.

13.4 Data analysis considerations

13.4.1 Dataset analyzed

13.4.1.1 Treatment group considered for statistical analysis

For all efficacy and safety analyses, patients will be included in the treatment group to which they were originally allocated by the IVRS.

13.4.1.2 Populations to be analyzed

The intent-to-treat (ITT) population will be used for all efficacy and safety analyses. This will consist of all randomized patients irrespective of whether the patient actually received study drug or the patient's compliance with the study protocol, in the treatment group assigned by the IVRS system. A patient will be considered randomized as soon as a treatment kit number is assigned by IVRS.

13.4.1.3 General statistical approach

All statistical tests will be two-sided.

All summary tables for quantitative parameters will display mean, standard deviation, median, range (minimum and maximum), as well as number of missing data (if relevant). All summary tables for qualitative parameters will display counts, percentages and number of missing data if relevant.

Baseline data are defined as the last measurement performed before the first study drug intake.

13.4.2 General convention

13.4.2.1 General rules for handling of missing, unused or inconsistent data

In general, missing values will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data analyses and presentations. Specific rules for handling missing efficacy data are described in Section 13.7.1.2.1.

13.4.2.2 Other specific conventions

13.5 Demographic and baseline characteristics

13.5.1 Patient demographic characteristics, medical history and diagnoses

Baseline characteristics will be described using the ITT population. Demographics, medical history and other baseline variables will be summarized as appropriate to the type of data.

13.5.2 Previous medications

In order to further characterize the study population, the incidence of the use of selected medications (statins, antihypertensive agents, antidiabetic agents and antiplatelet agents) at the time of randomization will be summarized.

13.6 Investigational Product and concomitant therapy

13.6.1 Investigational Product

13.6.1.1 Extent of exposure

The duration of study drug treatment (accounting for permanent discontinuation) will be summarized. The number of patients on treatment over time will be summarized. The total patient years on study drug will also be calculated

13.6.1.2 Measurement of treatment compliance

Treatment compliance for each patient will be calculated as the number of days study drug was actually taken (ie, number of days on treatment minus days of temporary discontinuation) divided by the number of days of follow-up, allowing for early permanent discontinuation of study drug when applicable. Study drug discontinuation is defined as a minimum of 5 consecutive days without study drug intake. The percentage of patients at least 80% compliant will also be reported.

13.6.2 Concomitant medication/therapy

The incidence of the use of selected concomitant medications (statins, antihypertensive agents, antidiabetic agents, and antiplatelet agents) will be summarized in each treatment group.

13.7 Efficacy/activity analysis

13.7.1 Primary efficacy variable(s)

13.7.1.1 Description of the primary variable(s)

The primary efficacy endpoint is the composite cluster of the first occurrence, over the duration of study (randomization to study end date inclusive), of the following adjudicated events:

- Any MI,
- Any stroke,
- Cardiovascular death

as validated by the CEC.

13.7.1.2 Primary analysis

13.7.1.2.1 Handling of dropouts or missing data

All randomized patients will be included in the primary ITT efficacy analysis. Patients not reaching the primary efficacy endpoint by the study end date, or before their last assessment for patients lost to follow-up, will be censored at the date of their last assessment visit.

13.7.1.2.2 Data transformation before analysis, if any

No data transformation will be applied to raw data.

13.7.1.2.3 Main statistical model and adjustment for covariates

For the primary analysis, all adjudicated events occurring from randomization to the study end date (inclusive) will be counted, including events occurring after early permanent discontinuation of study drug. The proportion of patients remaining event-free over time will be displayed in the form of survival curves using the Kaplan-Meier method and analyzed (primary analysis) using a two-sided log-rank test. Statistical significance will be claimed if the computed p-value is equal to or less than 0.05.

The number and percentage (crude rate) of patients experiencing a primary endpoint will be summarized.

13.7.1.2.4 Multiple comparisons/multiplicity

If the primary efficacy reaches statistical significance, then the two secondary endpoints will be formally tested at the 5% level in a hierarchical (step-down) procedure. First the MI, stroke, cardiovascular death or hospitalization endpoint will be tested, and then, if this reaches significance, the all-cause mortality endpoint will be tested.

13.7.1.2.5 Other analyses for primary variable(s)

In order to further investigate the primary endpoint the following analysis will be done:

Subgroup analysis: The incidence of the primary efficacy endpoint will be summarized by a number of covariates including age, gender, and race to examine their potential effects. Each of these factors will be analyzed statistically using a Cox proportional hazards model incorporating terms for treatment, the covariate and the treatment-by covariate interaction. The number of patients with outcomes, estimated hazard ratios, and associated 95% confidence intervals will be calculated within each of the subgroups generated by these analyses.

13.7.2 Secondary/other efficacy variables

13.7.2.1 Description of secondary/other variables

- Secondary endpoint: The composite cluster of the first occurrence, over the duration of study (randomization to study end date inclusive), of the following cluster of events:
  - Any MI,
  - Any stroke
  - Cardiovascular death
  - Hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure)

- Other efficacy endpoints:

  - All-cause mortality

  - The following events taken separately will also be assessed:
    - Any MI
    - Any stroke
    - Cardiovascular death
    - Hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure).

  - The change from baseline measurement for waist circumference and weight will be assessed.

13.7.2.2 Statistical analysis of secondary/other variables

The secondary and other endpoints will be analyzed using the same statistical methodology as for the primary efficacy endpoint (except for weight and waist circumference).

13.8 Safety analysis

For this morbidity/mortality trial, a benefit risk assessment is important. For this purpose safety analyses will be conducted on the same population (ITT) and using the same evaluation period as for efficacy analyses. (ie, from randomization until study end date)

13.8.1 Adverse Events

13.8.1.1 Definitions

All adverse events recorded during the study will be coded according to Medical Dictionary for Regulatory Activities.

13.8.1.2 Adverse Events

Summaries will be done for the following types of AE:

- Number (%) of patients with any AE,
- Number (%) of patients with any SAE,
- Number (%) of patients permanently withdrawn from treatment due to AE,

All summaries will display, by treatment group, the overall frequency of patients with events, the frequency of patients with events within each primary system organ class and by preferred terms. For each preferred term and each system organ class a patient will be counted only once. For summaries on severe or drug-related AE, for a given patient, the highest severity or relationship for a specific preferred term will be considered.

13.8.1.3 Deaths and Serious Adverse Events

Serious adverse events and events leading to death (non-CV deaths) will be summarized overall and by primary system organ class and preferred term.

13.8.1.4 Adverse Events leading to treatment discontinuation

Adverse events leading to treatment discontinuation will be summarized overall and by primary system organ class and preferred term.

13.8.2 Clinical laboratory evaluations

The analysis will focus on potentially clinically significant abnormality (PCSA) values. Patients with PCSA for each test will be identified. Number and percentage of patients with PCSA at any post-randomization time point will be used to summarize each clinical laboratory test. The summaries will include patients who have at least one laboratory test performed after the first study drug administration and, when required by the definition of the abnormality, with an available baseline value. For these descriptions the baseline value will be the last available measure before study drug intake.

Descriptive statistics will also be used to summarize the values and changes from baseline for each treatment group across time.

13.8.3 Vital signs

Assessment of vital signs will be carried out as described in Section 13.8.2.

14. SUBSTUDIES

There will be a Metabolic Substudy conducted in selected sites, encompassing approximately 3000 patients. This substudy will assess rimonabant's effects on fasting plasma glucose, insulin, HbA1c, triglyceride, HDL-cholesterol, and LDL-cholesterol levels compared to placebo, in a subset of CRESCENDO patients. Samples will be obtained at baseline and every six months thereafter, and at the End of Study visit. This study will be the subject of a separate protocol (Appendix 9) and informed consent.
Other substudies of high scientific merit will be conducted based on the recommendation of the Executive Committee. Substudies planned include a Biomarker Substudy and a Genomics Substudy. These studies will be the subject of separate protocols (Appendix 10 and Appendix 11) and informed consents.
The analysis and reporting of the substudies will be totally separate from the main study.

15. ETHICAL AND REGULATORY STANDARDS

15.1 Ethical principles

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP). Those Investigators participating as leaders in this trial, including members of the Executive and Operations Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

15.2 Laws and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

15.3 Informed consent

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial, including the written information given approval/favorable opinion by the Institutional Review Board/Ethics Committee (IRB/EC).

Prior to a patient's participation in the clinical trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc.), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC for approval/favorable opinion.

15.4 Institutional Review Board/Independent Ethics Committee (IRB/EC)

The Investigator must submit this Clinical Trial Protocol to the appropriate IRB/EC, and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/EC composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/EC approval/favorable opinion.

Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the IRB/EC. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/EC.

If requested, a progress report is sent to the IRB/EC annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

16. STUDY MONITORING

16.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and by study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.

If any particular circuits have to be defined (e.g., e-CRF, Fax), particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be timely appointed and listed. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a Clinical Trial Protocol and all necessary information.

16.2 Responsibilities of the Sponsor

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements, and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, outcome events documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

16.3 Source document requirements

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/EC), and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound

by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

16.4 Use and completion of Case Report Forms (CRFs) and additional requests

It is the responsibility of the Investigator to maintain adequate and accurate CRFs designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data; a black ball point pen should be used to ensure the clarity of the reproduced copy of all CRFs, which should be faxed within 48 hours of completion or any modification to the Central Database number.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated, and the corrected CRF should be faxed again to the Central Database number.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. Unresolved requests will be faxed to the Investigator at least every 2 weeks. Modified CRFs following resolution of the queries should be faxed again to the Central Database number.

17. ADMINISTRATIVE RULES

17.1 Curriculum Vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

17.2 Record retention at study site(s)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents within the fifteen (15) year period following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

18. CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/EC) is expressly permitted, the IRB/EC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

19. PROPERTY RIGHTS

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.
The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The complete verified database will be shared with the Operations Committee, which shall have full access to all data.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.
As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

20. DATA PROTECTION

- The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

21. INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy that covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements.

An insurance certificate will be provided to the Investigator in countries requiring this document.

The insurance of the Sponsor does not relieve the Investigator and the collaborators of any obligation to maintain their own liability insurance policy as required by applicable law.

22. SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

23. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

23.1 Decided by the Sponsor in the following cases:

- In the event the results of the Clinical Trial do not appear to be scientifically convincing to the Sponsor;
- If the aim of the Clinical Trial has become outdated or is no longer of interest;
- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for GCP;
- If the total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

23.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/EC) and Health Authorities should be informed.

24. CLINICAL TRIAL RESULTS

- The Sponsor will be responsible for preparing a Clinical Study Report;
- When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

25. PUBLICATIONS AND COMMUNICATIONS

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked and validated data in order to ensure the accuracy of the results.

At least thirty (30) days in advance of proposed submission, the primary author should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary,

delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

In multicenter studies conducted by an Executive Committee, with an Operations Committee, it is those bodies that are responsible for presentations and/or publications. The Committee must send a copy of the manuscript or abstract to the Sponsor for review at least thirty (30) days before submission.

All study participants (Investigators and Committee members) give full authority to the Executive Committee for primary presentation and/or primary publication of the results in the name of wholehearted collaborators. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by the Operations Committee and make reference to the study and the primary publication. The final decision to publish articles and their content will be made by the Operations Committee after prior notice to the Sponsor, allowing their review and comments on all manuscripts (at least thirty days in advance of submission, unless a mutual agreement allows a shorter notice).

26. CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the IRB/EC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/EC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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28. APPENDICES

Appendix 1: THE CLEVELAND CLINIC CARDIOVASCULAR COORDINATING CENTER (C5) AND STUDY SPONSOR RESPONSIBILITIES

1. C5 Project Team responsibilities

The C5 Project Team located at the Cleveland Clinic Foundation, is independent of the Sponsor and its primary function is to facilitate and oversee the execution of the study in collaboration with the Sponsor. The C5 Project Office will keep the Operations Committee appraised of the progress and conduct of the trial and will provide ongoing administrative support to the Clinical Events Committee and other committees.

- Key members of the C5 Project Team are:
  - Project Managers
- Oversight activities of the C5 Project Team include the following:
  - Coordination of protocol and CRF review at the Cleveland Clinic
  - Site Management for US sites
    - Review of monitoring visit reports (selection, initiation and interim reports)
    - Direct communication with the sites regarding the trial and any relevant issues (calls documented in a database)
    - Re-training of sites staff in case of turnover
    - Distribution of a monthly newsletter
  - Maintenance of a hot-line service for medical questions, including medical advice if unblinding is considered
  - Clinical Events Committee (CEC):
    - Development of CEC review forms and CEC review instructions
    - Appointment of medical reviewers blinded to treatment at C5 for validation of events reported in English (approximately 50% of adjudicated events)
    - Appointment of decentralized physician reviewers in each of the non-English languages
    - Coordination of the ongoing medical review of adjudicated endpoints
    - Reviewers contracts and payments
  - Executive Committee, Operations Committee and National Coordinators:
    - Coordination, organization of meetings, distribution of documents and minutes
    - Contracts and honorarium payments
  - DMC:
    - Support for organization of DMC meetings
    - Contracts and honorarium payments
  - Prepare final study manuscript for publication

2. Study Sponsor responsibilities

The Study is being sponsored by Sanofi-Synthelabo Recherche, and monitored by Sanofi-Synthelabo Recherche. As such, they will share legal and regulatory responsibilities for the conduct of the study and control and distribution of the investigational agent, rimonabant or its placebo. In fulfilling these responsibilities according to sanofi-aventis standard operating procedures, the Sponsor's activities include the following:

- Medical Input
  - participate at the Operations Committee and the Executive Committee meetings or teleconferences
  - update the Clinical Investigator's Brochure at least annually
- Drug Supplies
  - manufacture and ship drugs and matching-placebos
  - release drug supplies to individual Clinical Centers after receipt of documentation at the Sponsor's regional centers
- Funding
  - provide indemnification letters as required
  - provide funding and contracting with Investigators for the conduct of the study.
- Regulatory
  - obtain all necessary documents from Investigators for regulatory filings
  - ensure initial, and then annual (when applicable) IRB/EC approval is obtained by Investigators
  - monitor compliance with all applicable national and local law
  - maintain and coordinate contact with national regulatory authorities
  - submit all necessary regulatory filings
  - oversee all communication between DMC and regulatory authorities to make certain it occurs in a timely manner
  - perform all statistical analysis and medical writing of clinical reports for registration applications
- Study Monitoring
  - develop a study monitoring plan
  - monitor clinical centers
  - ensure protocol adherence
  - assess timely completion and submission of Case Report Forms (CRFs) and support documents
  - monitor quality and homogeneity of all data processing activities
  - Quality Assurance audits of the study as needed
  - monitoring and overseeing the maintenance of study conduct according to ICH, GCPs, and all country-specific regulations
  - clarify queries or missing documents, including assisting C5 Project Team to clarify queries or missing documents from US sites
  - maintain necessary communication with all National Coordinators, Investigators and study personnel
- Data Management and Study Drug Allocation Procedure
  - develop and manage the Central Study Database, perform data entry and validate records in the fax acquisition system

- implement appropriate measures for data quality control
- implement and manage the central randomization system
- generate patient visit schedules for all centers
- compile and generate weekly study status reports for general distribution to all personnel involved in the study, centrally and locally

- Study Archives
  - maintain study archives
- Study Reporting
  - provide support to the Executive Committee for the primary scientific publication of the study
  - develop a clinical study report for registration purpose

Appendix 2: The Executive Committee

Responsibilities

The Executive Committee is composed of university-based and Sponsor-based scientists with clinical and methodological expertise. The committee has the overall responsibility for producing and conducting a scientifically sound study and ensuring accurate reporting of the study. In that capacity, the Executive Committee must address and resolve scientific issues encountered during the study. This committee will meet at least twice a year.

All proposed ancillary research investigations on patients enrolled must be approved by the Executive Committee. The primary scientific publication reporting the study results is the responsibility of the Executive Committee. Collaborating Investigators or members of the various study committees wishing to prepare secondary publications must submit proposals and manuscripts to the Executive for approval. The Sponsor reserves the right to review manuscripts prior to submission for publication in a scientific journal. The final decision on all publications will be the responsibility of the Operations Committee.

Membership

Expert members:

Name	Function	Expertise	Country
Eric J. TOPOL	Chairman	Cardiology	USA
Deepak L. BHATT	Member/International PI	Cardiology	USA
Marie-Germaine BOUSSER	Member/Investigator	Neurology	France
Keith A. A. FOX	Member/Investigator	Cardiology	UK
Eric COHEN	Member/Investigator	Cardiology	Canada
Mark A. CREAGER	Member/Investigator	Cardiology	USA
Jean-Pierre DESPRES	Member/Investigator	Obesity/Lipids	Canada
J. Donald EASTON	Member/Investigator	Neurology	USA
Christian W. HAMM	Member/Investigator	Cardiology	Germany
Gilles MONTALESCOT	Member/Investigator	Cardiology	France
Thomas A. PEARSON	Member/Investigator	Preventive Med	USA
P. Gabriel STEG	Member/Investigator	Cardiology	France

Company's members:

Christophe GAUDIN
Bernard JOB
Judith MURPHY
Susan SLATYLAK-CHEEKS

Appendix 3: The Operations Committee

Responsibilities

The Operations Committee is responsible for ensuring that study execution and management are of the highest quality. Issues relating to regulatory reporting are the responsibility of the Sponsor, although the Operations Committee is to be kept informed of these activities. The Operations Committee will determine its own guidelines and approve the criteria and guidelines of the other committees prior to commencement of the study. The Operations Committee will be responsible for publications.

The Operations Committee will convene regularly to discuss and report on the ongoing supervision of the study.

Membership

Eric J. TOPOL (Chairman)
Deepak L. BHATT (International PI)
Marie-Germaine BOUSSER (Member)
Keith A. A. FOX (Member)
Bernard JOB (sanofi-aventis) (Nonvoting member)
Christophe GAUDIN (sanofi-aventis) (Nonvoting member)
Judith H. MURPHY (sanofi-aventis) (Nonvoting member)
Nadine JURAN (C5 Project Team) (Nonvoting member)

Working procedure

The Operations Committee will need to determine its own working guidelines, especially regarding the decision-making process on specific aspects of the study conduct.

Appendix 4: The Clinical Events Committee (CEC)

Responsibilities

The Clinical Events Committee is charged with the responsibility for validating all reported primary efficacy outcomes and validating the classification of the cause of all deaths. The event adjudication process will be coordinated by C5.

Members of the Clinical Event Committee will be chosen based on their clinical expertise and language skills. It is expected that most languages will be represented by 2 cardiologists and 2 neurologists. Adjudicators will be trained at a preliminary meeting where study definitions will be reviewed and test cases performed to ensure uniform application of study definitions. Reported events will be adjudicated by at least one committee member. Dossiers of reported events will be prepared and distributed to committee members on a regular basis to ensure that events are adjudicated in a timely fashion. Each committee member will be requested to review the dossiers sent to him/her and acknowledge in writing his/her agreement/disagreement with the investigator's interpretation of events.

Definitions for Validation of Reported Outcome Events

Reported outcome events are all defined in the protocol and only these definitions should be used for adjudication.

- Adjudication of strokes will rely on neurologists in charge of validating such events and their classification as ischemic strokes (IS), hemorrhagic strokes or strokes of unknown cause. Hemorrhagic strokes will be further classified as PICHs and non-PICHs by a Central Neurologist.
- Adjudication of myocardial infarctions (MI) will rely on cardiologists in charge of validating such events and their classification as Q wave MI or non-Q wave MI.
- Adjudication of the cause of death will be performed by the following:
  - neurologists for validation of suspected fatal strokes.
  - cardiologists for all other deaths classified as fatal MI, other CVD, or non-CVD

Fatal strokes, fatal MIs, and other cardiovascular deaths (including unknown causes) will constitute cardiovascular deaths.

Review process for reported efficacy outcome events

- First adjudicator agrees with Investigator's report of outcome event:
  - Agreement acknowledged in writing and filed at C5
  - Event Adjudication database updated accordingly
  - Investigator's report of outcome event accepted
  - Adjudication complete

- First adjudicator disagrees with Investigator's report of outcome event:
  - Disagreement or uncertainty acknowledged in writing
  - Event Adjudication database updated accordingly
  - Outcome event forwarded for review to second adjudicator who is unaware of prior adjudication
- If second adjudicator agrees with Investigator's report of outcome event:
  - Agreement acknowledged in writing and adjudication report filed at C5
  - Event Adjudication database updated accordingly
  - Investigator's report of outcome event accepted
  - Adjudication complete
- If second adjudicator disagrees with Investigator's report of outcome event and agrees with first adjudicator:
  - Disagreement acknowledged in writing and adjudication report filed at C5
  - Event Adjudication database updated accordingly
  - Adjudicator's report of outcome event accepted
  - Adjudication complete

- If second adjudicator is uncertain:
  - Stalemate acknowledged in writing
  - Event Adjudication database updated accordingly
  - Outcome event forwarded to Chairman of Clinical Events Committee for resolution. Final decision mandatory at this stage
  - Chairman's decision acknowledged in writing and reports filed at C5
  - Adjudication complete

The Clinical Events Committee and C5 will establish detailed written guidelines for the event adjudication process. The CEC will prepare a manual that will describe the quality assurance procedures.

The Clinical Events Committee will meet initially for orientation and training. Afterwards, meetings will be held as required to address and resolve committee policy issues.

Membership

Chairman : Sorin Brener

Members will be supplemented as necessary in order to ensure that two cardiologists and two neurologists are available to represent most languages of study participant countries.

Appendix 5: The Data Monitoring Committee (DMC)

General Overview

The Study will be conducted in a double-blind manner in which patients and treating physicians are blinded. The trial management team, including Operations Committee, Executive Committee, Clinical Events Committee, the C5 Project Team and the Sponsor will also be blinded with respect to treatment allocation.

To facilitate its responsibilities, the DMC will have an Associated Statistician who will receive study data directly from the Central Database and who will remain independent of the trial management team. The DMC Associated Statistician is not a member of the DMC, but presents data to the committee and is responsible to the Chairman.

The DMC Associated Statistician, being unblinded, will not be able to edit/alter any part of the Central Database.

Other than the Associated Statistician, routine access to the treatment code will be restricted to the Chairman of the DMC, except for emergency unblinding on a case-by-case basis, if required for regulatory purpose.

DMC Responsibilities

Primary:

1. Regular review of safety data including serious adverse events, as defined in the DMC Charter
2. Feedback to the Chairman of the Operations Committee

Secondary:

1. Respond to special requests from regulatory authorities or IRB/ECs
2. Recommendations for protocol amendments

Verification of final analysis of the study will be done by the DMC Associated Statistician.

Safety Review

Recommendation to stop a trial early for safety reasons is, by definition, a subjective judgment. The DMC is composed of eminent clinicians and methodologists who are experienced with clinical trials and can be relied upon to exercise good judgment in weighing the potential risks and benefits to patients as data accumulate in this trial.

The DMC will fulfill its responsibility to monitor the safety of patients by conducting formal reviews of accumulated safety and efficacy data. These reviews will normally occur at regular intervals as defined in the DMC charter, however, in case of specific concerns, ad-hoc meetings can be set up. The DMC Associated Statistician will prepare a report of aggregate data summaries and other data, where appropriate, for each treatment group. This report will be circulated to each member of the DMC at least one week prior to their collective review. The committee will then convene, either by face-to-face meeting or by telephone conference call, to make its recommendation to the Operations Committee with respect to continuance of the trial or any changes to the conduct of the trial. A formal written communication to the Chairman of the Operations Committee will then follow. Minutes of all official meetings of the DMC and any recommendations will ultimately be part of the Sponsor's master files after the study is over and the results are known (archives).

The report of data summaries and listings will include information on both safety and efficacy parameters, together with status reports designed to show the extent to which the trial is being executed according to protocol. Included among the safety data will be (a) all deaths (b) SAEs and (c) other adverse events as requested by the DMC. Efficacy summaries will provide information on the occurrence of all study outcomes. The outcome events are considered as distinct from adverse events and summarized separately. At each review by the DMC, consideration of a decision to stop the trial on grounds of patient safety will weigh the current evidence of differences between treatments regarding adverse effects (as expressed by mortality, adverse event reports, etc) against emerging trends in efficacy. Providing efficacy data at each of these routine safety reviews does not constitute a formal interim analysis of efficacy, and these analyses will not, in and of themselves, be used for stopping the trial (see next section).

Data for the safety review will be made available from the Central Database on a quarterly basis (roughly three weeks prior to DMC meetings). Serious adverse events are required to be reported rapidly to the Sponsor and will be entered into a separate Pharmacovigilance database that will also be transferred to the DMC Associated Statistician, in addition to the Central Database. Primary outcome events will be reviewed by the Clinical Events Committee on an ongoing basis to determine if each reported event meets the defined criteria for a study outcome event. The DMC will review data on all reported outcome events. Additional summaries will show the results of the Clinical Event Committee's judgments on the subset of reports that has been reviewed by this committee.

Feedback From the DMC

a) To the Operations Committee

All communications between the Operations Committee and the DMC will be through the office of the Chairman of the Operations Committee and be documented in writing.

Information provided by the DMC may be confidential and must be kept so within the Operations Committee.

The Operations Committee may request supplementary information from the DMC, if necessary. The DMC Chairman will consider all such requests.

b) To/From the Sponsor

Special requests from any national regulatory authority requiring DMC input will be forwarded by the Sponsor to the Chairman of the Operations Committee. Any requests that cannot be performed by the Chairman of the Operations Committee will be forwarded to the Chairman of the DMC to be done by the DMC Associated Statistician. New preclinical and clinical information from other trials will be provided to the DMC in an updated Investigator's Brochure.
Representatives of the study organization will discuss the content and timing of such feedback with the agencies concerned. All necessary analyses and reports will be sent in a timely fashion. The Chairman of the Operations Committee and the Sponsor's regulatory department will be copied on the covering letter to any reports provided to individual regulatory agencies. However, no unblinded reports will be sent to any organization other than the regulatory agency that requested it.

Protocol Change Recommendations

It is possible that the DMC might suggest changes in the protocol as a result of their reviews. Any suggestions will be provided in writing to the Chairman of the Operations Committee, including a detailed rationale with the anticipated consequences in terms of study bias.

Confidentiality

Information provided to the DMC is strictly confidential and must not be disclosed other than through the mechanisms described above. In particular, members of the DMC cannot publish any information derived from its privileged access to the study data without the approval of the Operations Committee.

Membership

Chairman	**Robert L. FRYE, MD**
Members	Kerry L. LEE, Ph.D Robert HARRINGTON, MD Lawrence M. BRASS, MD Jean-Louis IMBS, MD Charles MCCARTHY, Ph.D Albert SCHOEMIG, MD
Independent Statistician	Marc BUYSE, Sc.D

Appendix 6: Waist Circumference Measurement

Waist is taken at the midpoint between the lower rib margin and the iliac crest in cms; 3 separate measurements will be performed and recorded in the CRF at each visit where waist circumference is recorded.

Waist circumference >88 cm in women or >102 cm in men define abdominal obesity (ref NCEP ATP III definition of the metabolic syndrome)

- The circumference should preferably be measured on subjects while they are semi-clothed, i.e. waist uncovered with the subjects wearing underclothes only. If it is not possible to follow this procedure, the alternative is to measure the circumference on subjects without heavy outer garments with all tight clothing, including the belt, loosened and with the pockets emptied.
- Patients should stand with their feet fairly close together (about 12-15 cm) with their weight equally distributed on each leg. Participants should be asked to breathe normally and at the time of the reading of the measurement asked to breath out gently. This will prevent subjects from contracting their muscles or from holding their breath.
- A plastic metric tape should be used. The tape should be held firmly and its horizontal position should be ensured. It is recommended that the observer sit beside the participant while the readings are taken. The tape should be loose enough to allow the recorder to place one finger between the tape and the subject's body. The importance of the tightness of the tape should be emphasized in training.

Appendix 7: Ankle-Brachial Index measurement

a) Measure highest systolic reading in both arms
   1. Record first Doppler sound as cuff is deflated
   2. Record at the radial pulse
   3. Use highest of the two arm pressures

b) Measure systolic readings in both legs
   1. Cuff applied to calf
   2. Record first Doppler sound as cuff is deflated
   3. Use Doppler ultrasound device

c) Record dorsalis pedis (DP) pressure

d) Record posterior tibial (PT) pressure
   1. Use highest ankle pressure (DP) or (PT) for each leg

e) Calculate ratio of each ankle to brachial pressure
   1. Divide each ankle by highest brachial pressure

Appendix 8: Intima-Media Thickness measurement

Carotid intima-media thickness (IMT) is a marker of early arterial change of the arterial walls including atherosclerosis and/or vascular hypertrophy, detected by B-Mode ultrasonography.

1. Recommendations for ultrasonographic examinations:

   - Machines equipped with 5 or 7 MHz transducers
   - Subjects in the supine position
   - ECG signal used for synchronizing the image analysis to the end of the diastole
   - Doppler ultrasound used for vessel identification (and information on blood flow velocity)
   - Carotid artery scanned at the level of the bifurcation, with the head turned to the opposite side (e.g. to the right for left carotid artery)
   - Examined region:
     - 30 mm of the common carotid artery
     - carotid bulb
     - 10 mm each of the internal and external carotid arteries
   - Regions scanned with both longitudinal and transverse projections, in order to assess the occurrence of plaques
   - Three "frozen" images recorded for assessment of intima-media thickness and lumen diameter
   - Optimal image projection considered to be achieved when ultrasound beams are perpendicular to the far vessel wall

2. Recommendations for assessments of intima-media thickness[1] and lumen diameter[2]

   - Ultrasonographic images analyzed with a computerized system
   - Intima-media thickness measured in a 10 mm long segment just proximal to the carotid bulb in the common carotid artery
   - Calculation by the computer program of the minimum, maximum and mean values of intima-media thickness from three separate images

3. Assessments of plaques

   - A plaque is defined as a distinct area with an intima-media thickness exceeding twice that of the neighboring sites

[1] Intima-media thickness is defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall

[2] Lumen diameter is defined as the distance between the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall

- Classification of plaques, according to a four-graded semi-quantitative scale of their size/severity:
  - Grade 0: no plaque
  - Grade 1: small localized plaque/wall thickening
  - Grade 2: moderate plaque with <50% lumen diameter stenosis
  - Grade 3: circumferential and/or large plaque with ≥50% lumen diameter stenosis
- Plaques detection must be focused on the distal part of the common carotid artery, the carotid bulb or in the proximal parts of the internal or external carotid artery.

Appendix 9: Metabolic Substudy

Protocol Number: Substudy of CRESCENDO Study Number EFC5826
Date: 19 August 2005

Substudy of CRESCENDO Study Number EFC5826: CRESCENDO

Metabolic Substudy

Principal Investigator:
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The Cleveland Clinic Foundation
9500 Euclid Ave., Cleveland Ohio 44195 USA

SUBSTUDY PROTOCOL ACKNOWLEDGEMENT

I have read this Substudy of CRESCENDO Study Number EFC5826: CRESCENDO **Metabolic Substudy** and understand that it and an accompanying informed consent must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

_____ _____

Investigator's printed name and signature *Date*

1. INTRODUCTION

Rimonabant is being studied in CRESCENDO to see whether its use is associated with a reduction in myocardial infarction, stroke, or cardiovascular death in abdominally obese patients at increased risk for cardiovascular events. In earlier trials, rimonabant use has been shown to be associated with an increase in HDL-cholesterol, a decrease in triglycerides, and an improvement in insulin sensitivity and glycemic control. This substudy is being conducted to demonstrate that rimonabant has beneficial effects on these metabolic risk factors for cardiovascular events, in conjunction with a demonstrable beneficial effect on cardiovascular event.

2. PRIMARY OBJECTIVE

To evaluate the effect of rimonabant 20 mg OD on fasting HDL-cholesterol, fasting LDL-cholesterol, fasting triglyceride, fasting plasma glucose, fasting insulin, and fasting HbA1c levels.

3. STUDY DESIGN

Patients randomized in the multinational, multicenter, double-blind, placebo-controlled parallel group CRESCENDO study at selected sites will be asked to participate in this substudy. Once written informed consent is obtained, patients will have blood drawn, after an overnight fast, at baseline, at every 6-month visit, and at the end of study visit. Blood samples will be analyzed at a Central Laboratory, and the Investigators, patients, and Sponsor personnel will be blinded to the results.

4. SELECTION OF PATIENTS

Sites selected to participate in this substudy will have IRB/EC approval for the main CRESCENDO study and for this substudy and separate informed consent. All subjects must meet eligibility criteria for the main CRESCENDO study, must give written informed consent for that study, and must also give written informed consent for this substudy. Approximately 3000 patients will be expected to participate in this substudy. There are no separate inclusion or exclusion criteria for this substudy, besides the requirement for written informed consent. Patients who have consented to participate in the main study but refuse participation in this substudy will be allowed to continue in the main study.

5. STUDY PROCEDURES

After an overnight fast, patients will have blood samples drawn for HDL-cholesterol, LDL-cholesterol, triglyceride, plasma glucose, insulin, and HbA1c measurements at baseline, at every 6-month visit, and at the end of study visit. An additional blood sample will be drawn for other metabolic testing that may become indicated. Blood samples will be processed at the site in accordance with directions provided by the Central Laboratory, and shipped to the Central Laboratory facility for analysis. The results of these analyses will be maintained by the Central Laboratory, and the results, coded by patient's initials,

gender, and date of birth, patient's study number, and date blood sample was obtained, will be sent to the Sponsor for loading into the study database. The Investigators and the patients will be blinded to the results.

6. WITHDRAWAL OF CONSENT

Patients may withdraw consent from participation in this substudy at any time. If they do so, they may continue full participation in the main CRESCENDO study. If they withdraw from study medication, they may continue in this substudy.

7. PRIMARY STATISTICAL ANALYSIS

Changes in fasting HDL-cholesterol, fasting LDL-cholesterol, fasting triglyceride, fasting plasma glucose, fasting insulin, and fasting HbA1c levels at each point in time from baseline will be analyzed and the results compared between the rimonabant and placebo groups, using an analysis of covariance (ANCOVA), with the baseline value as covariate, with a significance level of 0.05.

8. SAFETY REPORTING

Adverse events and serious adverse events will be captured and reported in accordance with the main CRESCENDO study (Section 10). Since Investigators and the Sponsor will be blinded to the results of these laboratory tests, abnormal results will not be reportable as adverse events.

9. ADMINISTRATION

9.1 Informed Consent

A separate informed consent will be obtained from CRESCENDO patients who voluntarily agree to participate in the Metabolic Substudy. The Informed Consent Form reflecting this substudy will be submitted for review and approval to the IRB/EC charged with this responsibility.

9.2 Confidentiality

Blood samples collected for this substudy will be labeled with the patient's initials, gender, and date of birth, study number, site number, and date of collection. Data handling by the Sponsor will be in accordance with that described in the main CRESCENDO protocol (Section 18), and every effort will be made to protect patient confidentiality. In case the results are published, they will be done so anonymously.

9.3 Institutional Review Board/Ethics Committee

This Metabolic Substudy, the Informed Consent Form for this Metabolic Substudy, and any advertisement for patient recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

9.4 Records Retention

Investigators must retain records pertaining to this substudy as described in the main CRESCENDO study protocol (Section 17.2).

Appendix 10: Biomarker Substudy

Protocol Number: Substudy of CRESCENDO Study Number EFC5826
Date: 19 August 2005

Substudy of CRESCENDO Study Number EFC5826: CRESCENDO Biomarker Substudy

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Cleveland Clinic Cardiovascular Coordinating Center
The Cleveland Clinic Foundation
9500 Euclid Ave., Cleveland Ohio 44195 USA

SUBSTUDY PROTOCOL ACKNOWLEDGEMENT

I have read this Substudy of CRESCENDO Study Number EFC5826: CRESCENDO **Biomarker Substudy** and understand that it and an accompanying informed consent must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

_____ _____

Investigator's printed name and signature *Date*

1. INTRODUCTION

Rimonabant is being studied in CRESCENDO to see whether its use is associated with a reduction in myocardial infarction, stroke, or cardiovascular death in abdominally obese patients at increased risk for cardiovascular events. In several other trials, several inflammatory biomarker cytokines have been associated with an increased risk of cardiovascular events. One such marker is C-reactive protein (CRP). In earlier studies, rimonabant use has been shown to be associated with a decrease in CRP. This substudy is being conducted to assess rimonabant's effects on hs-CRP and on other inflammatory markers, including soluble CD40 ligand (sCD40L), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), soluble vascular cellular adhesion molecule-1 (sVCAM-1), P-selectin, and myleoperoxidase, in this patient population at risk for cardiovascular events. In addition, there are other cytokines produced by adipocytes that have been shown to be abnormal in overweight/obese patients, such as adiponectin, resistin, leptin, omentin, osteonectin, and visfatin. These abnormalities may also be associated with insulin resistance, an increase in inflammatory markers, and an increase in atherogenesis and cardiovascular risk. This substudy will also explore whether rimonabant has beneficial effects on these adipocytokines.

2. PRIMARY OBJECTIVE

To evaluate the effect of rimonabant 20 mg OD on hs-CRP, sCD40L, IL-6, PAI-1, sVCAM-1, P-selectin, myeloperoxidase, adiponectin, resistin, leptin, omentin, osteonectin, and visfatin.

3. STUDY DESIGN

Patients randomized in the multinational, multicenter, double-blind, placebo-controlled, parallel group CRESCENDO study at selected sites will be asked to participate in this substudy. Once written informed consent is obtained, patients will have blood drawn at baseline, at every 6-month visit, and at the end of study visit. Blood samples will be analyzed at a Central Laboratory, and the Investigators, patients, and Sponsor personnel will be blinded to the results.

4. SELECTION OF PATIENTS

Sites selected to participate in this substudy will have IRB/EC approval for the main CRESCENDO study and for this substudy and separate informed consent. All subjects must meet eligibility criteria for the main CRESCENDO study, must give written informed consent for that study, and must also give written informed consent for this substudy. Approximately 3000 patients will be expected to participate in this substudy. There are no separate inclusion or exclusion criteria for this substudy, besides the requirement for written informed consent. Patients who have consented to participate in the main study but refuse participation in this substudy will be allowed to continue in the main study.

5. STUDY PROCEDURES

Patients will have blood samples drawn for hs-CRP, sCD40L, IL-6, PAI-1, sVCAM-1, P-selectin, myeloperoxidase, adiponectin, resistin, leptin, omentin, osteonectin, and visfatin measurements at baseline, at every 6-month visit, and at the end of study visit. An additional blood sample will be drawn to provide for any additional testing that may become indicated. Blood samples will be processed at the site in accordance with directions provided by the Central Laboratory, and shipped to the Central Laboratory facility for analysis. The results of these analyses will be maintained by the Central Laboratory, and the results, coded by patient's initials, gender, and date of birth, patient's study number, and date blood sample was obtained, will be sent to the Sponsor for loading into the study database. The Investigators and the patients will be blinded to the results.

6. WITHDRAWAL OF CONSENT

Patients may withdraw consent from participation in this substudy at any time. If they do so, they may continue full participation in the main CRESCENDO study. If they withdraw from study medication, they may continue in this substudy.

7. PRIMARY STATISTICAL ANALYSIS

Changes in hs-CRP, sCD40L, IL-6, PAI-1, sVCAM-1, P-selectin, myeloperoxidase, adiponectin, resistin, leptin, omentin, osteonectin, and visfatin levels at each point in time from baseline will be analyzed and the results compared between the rimonabant and placebo groups, using an analysis of covariance (ANCOVA), with the baseline value as covariate, with a significance level of 0.05.

8. SAFETY REPORTING

Adverse events and serious adverse events will be captured and reported in accordance with the main CRESCENDO study (Section 10). Since Investigators and the Sponsor will be blinded to the results of these laboratory tests, abnormal results will not be reportable as adverse events.

9. ADMINISTRATION

9.1 Informed Consent

A separate informed consent will be obtained from CRESCENDO patients who voluntarily agree to participate in the Biomarker Substudy. The Informed Consent Form reflecting this substudy will be submitted for review and approval to the IRB/EC charged with this responsibility.

9.2 Confidentiality

Blood samples collected for this substudy will be labeled with the patient's initials, gender, and date of birth, patient's study number, and date of collection. Data handling by the Sponsor will be in accordance with that described in the main CRESCENDO protocol (Section 18), and every effort will be made to protect patient confidentiality. In case the results are published, they will be done so anonymously.

9.3 Institutional Review Board/Ethics Committee

This Biomarker Substudy, the Informed Consent Form for this Biomarker Substudy, and any advertisement for patient recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

9.4 Records Retention

Investigators must retain records pertaining to this substudy as described in the main CRESCENDO study protocol (Section 17.2).

Appendix 11: Substudy of CRESCENDO Study Number EFC5826: CRESCENDO Genomics Blood Sample Substudy

Protocol Number: Substudy of CRESCENDO Study Number EFC5826
Date: July 11, 2005

Substudy of CRESCENDO Study Number EFC5826: CRESCENDO Genomics Blood Sample Substudy

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Executive Committee Chair:
Prof. Eric J. Topol, MD
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Telephone (office): 1-216-445-9490
Fax: 1-216-445-9595

Cleveland Clinic Cardiovascular Coordinating Center
The Cleveland Clinic Foundation
9500 Euclid Ave., Cleveland Ohio 44195 USA

SUBSTUDY PROTOCOL ACKNOWLEDGEMENT

I have read this Substudy of CRESCENDO Study Number EFC5826: CRESCENDO **Genomics Blood Sample Substudy** and understand that it and an accompanying informed consent must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

_____ _____

Investigator's printed name and signature *Date*

1. STUDY OBJECTIVES

Primary Objective:

The primary objective of the CRESCENDO Genomics Blood Sample Substudy is to collect blood samples that may be used for future hypothesis generating and hypothesis testing research from subjects enrolled in CRESCENDO Protocol Study Number EFC5826.

Research that may be conducted on samples collected from this protocol or in combination with samples from other protocols can explore:

1) how variations in genes associate with clinical outcomes, eg, drug metabolizing enzyme variants with either pharmacokinetic endpoints or other clinical responses;
2) the associations among genetic variation, gene expression, and proteins and clinical conditions, such as obesity or metabolic disorders, and outcomes, such as MI, stroke, or cardiovascular death.

2. STUDY DESIGN

Subjects who have consented to participate in the CRESCENDO study and who voluntarily have given written informed consent for genomic sample collection will have a one-time blood sample drawn at any of the scheduled blood sample collections for clinical laboratory tests during this protocol. The sample will be shipped overnight (room temperature) the day it is collected to a designated central laboratory for processing. The sample will be stored frozen for banking at a Genetic Sample Bank (GSB) for genomic research studies. The sample will be shared with The Cleveland Clinic Foundation (CCF) and sanofi-aventis. These samples will be destroyed no later than 20 years from the date of collection.

3. SELECTION OF SUBJECTS

Genomic blood sample collection will be performed at CRESCENDO sites that permit genomic studies to be conducted in compliance with all applicable laws, rules, and regulations. Subjects enrolled in CRESCENDO Protocol Study Number EFC5826 at sites that have appropriate Institutional Review Board/Ethics Committee approval will be asked to participate voluntarily in the genomic research substudy. Subjects will be asked to read, understand, and sign an informed consent form designed for the purpose of collecting a one-time blood for genomic research. **Subjects will be informed that they will not be excluded from the CRESCENDO study if they do not wish to participate in the Genomic Blood Sample Substudy.**

4. ETHICS

The CRESCENDO Genomics Blood Sample Substudy can only be implemented where consistent with local law and only when the local IRB/Ethics Committee and Clinical Investigator have agreed to allow study subjects to participate in this portion of the study.

5. WITHDRAWAL OF SUBJECT CONSENT

5.1 Withdrawal of Subjects from Genomic Blood Sample Substudy

Subjects have, at any time, the option to withdraw consent for participation from

1) Only the Genomic Blood Sample Substudy independent of the CRESCENDO treatment protocol;

OR

2) Only the CRESCENDO study drug independent of the Genomic Blood Sample Substudy;

OR

3) Both the CRESCENDO clinical treatment and the Genomic Blood Sample Substudy.

Subjects who wish to withdraw their consent from the Genomic Blood Sample Substudy [ie, have their blood/DNA samples destroyed (see Section 5.2)] should contact the Investigator. The Investigator will submit a Sample Withdrawal Form to the GSB. The GSB will notify in writing CCF and sanofi-aventis.

It is possible that subjects may decide to withdraw consent from the CRESCENDO study drug but continue with their consent for the CRESCENDO Genomic Blood Sample Substudy. In such cases, the Investigator should inform subjects that their blood/DNA sample would remain stored at the GSB, CCF, and sanofi-aventis and will remain subject to genomic research.

5..2. Destruction of Blood Sample and Related Material

In the case of subjects who have withdrawn their consent for participation in the Genomic Blood Sample Substudy, the Investigator will send a Sample Withdrawal Form to the GSB. GSB will send a copy of the Sample Withdrawal Form to CCF and sanofi-aventis. CCF and sanofi-aventis, upon receipt of the Sample Withdrawal Form, will destroy all of the remaining blood sample and material obtained from the blood sample. A copy of the genetic sample destruction form is attached to this Appendix. CCF and sanofi-aventis will notify GSB in writing of the sample destruction. After all samples have been destroyed GSB will provide the Investigator with verification of the sample destruction. In the case of samples that have been partially analyzed the

remaining sample will be destroyed but CCF and sanofi-aventis shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

6. STATISTICAL CONSIDERATIONS

6.1 Sample Size Justification

No determined number of study subjects is required for genomic analysis.

6.2 Analysis

Joint exploratory data analysis may be performed in the future by the departments of Biostatistics and Data Management and Applied Genomics at CCF and sanofi-aventis to investigate if genetic variants (genotypes) are associated with clinical outcomes (phenotypes) such as but not limited to drug response, toxicity, time to disease progression and overall survival. The following potential analyses may be performed as appropriate:

- Examine demographic factors such as race/ethnic, age, and gender to determine appropriate stratification or adjustment for the analysis.
- Summarize allele and genotype frequencies from the sample with 95% confidence intervals.
- Explore the associations among genetic variation, expression of genes and proteins and clinical outcomes using methods like, but not limited to chi-squared tests, logistic regression, generalized linear models, non-parametric tree-based models, survival models or clustering algorithms. The associations may be expressed, where appropriate, using odds ratios with 95% confidence limits.

6.3 Blinding/Unblinding

Scientists performing the genetic analysis will be blinded to the patient identity as well as the CRESCENDO patient identification number. The sample will only be identified by a unique barcode. The code for identifying the corresponding CRESCENDO study identification number will be held by statisticians at C5 and Sanofi-Synthelabo. Only the site investigator will know the identity of the subject.

7. ADVERSE EVENT REPORTING

See Section 10 in the main CRESCENDO protocol.

8. ADMINISTRATION

8.1 Informed Consent

A separate informed consent will be obtained from study subjects who voluntarily agree to participate in the Genomic Blood Sample Substudy. The informed consent

form for genomic sample collection reflecting this substudy will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility.

8.2 Reports and Records

8.2.1 Confidentiality

CCF and sanofi-aventis will ensure that the confidentiality of research subjects who volunteer to participate is maintained and that the genomic analyses are conducted in compliance with all applicable laws, rules and regulations.

CCF and sanofi-aventis do not receive the identity of the subject when collecting data from the clinical trial and cannot associate the identity of the subject to the genomic research analyses. Therefore, any data from the genomic analyses that might be released into the public domain, for example in a scientific research publication, would be completely anonymous. This will ensure that the genetic information will not be used as a basis for discrimination.

8.2.2 Subject Rights

Study subjects can withdraw their consent to participate in the Genomic Blood Sample Substudy even after the sample has been shipped to the GSB. A study subject should contact their Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the bank and destroyed. For samples that have been partially analyzed the remaining sample will be destroyed but CCF and sanofi-aventis shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

The study subject agrees, when signing the informed consent form, that they will not be provided with the results from the genomic research, nor will the results be available to them at any time.

8.3 Institutional Review Board/Ethics Committee (IRB/EC)

This substudy, the informed consent form for genomic sample collection, and any advertisement for subject recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

8.4 Records Retention

Investigators must maintain records of subject CRESCENDO study identification number for 20 years after the sample is collected for purposes of notifying GSB of subjects who desire to withdraw consent.

This signed Genomics substudy protocol must be maintained with the original, signed CRESCENDO protocol.

SAMPLE WITHDRAWAL PROCEDURES

FAX TRANSMITTAL SHEET

FAX THIS COMPLETED PAGE TO:

WITHDRAWAL OF PERMISSION FOR USE OF SPECIMENS IN FUTURE GENETIC RESEARCH

This section is to be completed by either the investigator or the coordinator at the institution.

The study subject indicated below (Only identify the study subject using the study subject number; **DO NOT** provide any other identifying information such as the study subject's name or social security number) initially provided informed consent for his/her samples to be used for genomic research. After discussion with a study staff member at our institution, he/she has now indicated that he/she wants to withdraw consent for future genomic research and have his/her sample destroyed.

PROTOCOL NUMBER: CRESCENDO EFC5826 Genomics Blood Sample Substudy

CRESCENDO COUNTRY CODE: __ __ __ **CRESCENDO SITE NUMBER: __ __ __**

CRESCENDO SUBJECT NUMBER: __ __ __ **CRESCENDO SUBJECT INITIALS: __ __ __**

INVESTIGATOR NAME: _____ **INVESTIGATOR FAX: _____**

INVESTIGATOR SIGNATURE: _____

This section is to be completed by the Genetic Sample Bank and faxed back to the investigator.

CONFIRMATION OF GENETIC SAMPLE DESTRUCTION

The blood and related material derived from the blood sample obtained from the study subject indicated above has been destroyed. Please notify the study subject that this has occurred.

VERIFIED BY: _____ **DATE: _____**

PRINT NAME: _____