press release

TWO PIVOTAL STUDIES INDICATE ACOMPLIA™ (RIMONABANT) OFFERS A NOVEL APPROACH TO CARDIOVASCULAR RISK MANAGEMENT IN OVERWEIGHT/OBESE PEOPLE AND SMOKERS

RIO-LIPIDS AND STRATUS-US Study Results Announced Today at American College of Cardiology Annual Meeting

New Orleans, LA, March 9, 2004 - Early results of two Phase III studies with ACOMPLIA™ (rimonabant), the first in a new class of therapeutics called Selective CB_1 Blockers, indicate that overweight/obese patients with untreated dyslipidemia (high triglycerides and/or high total cholesterol/HDL cholesterol ratio) lost weight in one year while improving their lipid and glucose profiles, and that smokers who had previously unsuccessfully tried to quit smoking, were able to quit in 10 weeks without post cessation weight gain. The results of both the RIO-Lipids (**R**imonabant **I**n **O**besity) and STRATUS-US (**ST**udies with **R**imonabant **A**nd **T**obacco **US**e) trials were presented for the first time to the scientific community at the American College of Cardiology annual meeting in New Orleans, LA.

"Obesity and smoking are dangerous diseases that are reaching epidemic proportions around the world and are well known risk factors for cardiovascular diseases," said Chris Cannon M.D., Associate Professor of Medicine at Harvard Medical School and Associate Physician in the Cardiovascular Division of Brigham and Women's Hospital, Boston. "In addition, they frequently cluster with other metabolic risk factors such as dyslipidemia and diabetes. These results appear to show that rimonabant could become an important agent in the management of cardiovascular risk in these patient populations."

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What these risk factors have in common is that they all seem to be related to an over-stimulated Endocannabinoid System (EC System), a natural physiological system believed to play a role in maintaining energy balance through the regulation of food intake and energy expenditure. The EC system is also believed to play a role in tobacco dependence. In overweight/obese people, excessive eating and fat accumulation is associated with over-activation of the EC System, which also becomes unbalanced with chronic tobacco use. This leads to a series of signals transmitted by a receptor found in the EC System, the CB_1 receptor, which can be found in the brain and in other parts of the body (i.e. adipose tissue or "fat cells" which are involved in lipid and glucose metabolism). ACOMPLIA™ works by selectively blocking CB_1 receptors, helping to normalize the disrupted EC System. In overweight/obese people, this is thought to result in weight loss, reduced waist circumference and improvement of lipid and glucose metabolism. In those that smoke, ACOMPLIA™ thought to help people to stop smoking without significant post-cessation weight gain.

RIO-Lipids Study Findings

RIO-Lipids, an international multi-center, double-blind, placebo-controlled study, enrolled 1,036 overweight or obese patients with dyslipidemia (high triglycerides and/or high total cholesterol/HDL cholesterol ratio) and a Body Mass Index (BMI) between 27 and 40 kg/m^2. Patients were randomized to receive either a daily, fixed dose of ACOMPLIA™ 5 mg or 20 mg or placebo along with a reduced calorie diet for one year.

Patients treated for one year with rimonabant 20 mg per day lost 8.6 kg (almost 20 lbs) vs. a loss of only 2.3 kg (5 lbs) on placebo ($p<0.001$). Nearly 75% ($p<0.001$ vs. placebo) of patients treated for one year with ACOMPLIA™ 20 mg lost over 5% of their body weight as compared to 41.8% ($p = 0.002$ vs. placebo) of patients on ACOMPLIA™ 5 mg and 27.6% of patients in the placebo group. Moreover, 44.3% ($p<0.001$ vs. placebo) lost more than 10% of their body weight when treated for one year with ACOMPLIA™ 20 mg vs. 16.3% of patients on ACOMPLIA™ 5 mg or 10.3% of patients on placebo.

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In addition to weight loss, RIO-Lipids was designed to assess a number of associated important cardiovascular risk factors. All improvements in risk factors were statistically significant vs. the control group. In fact, the number of patients diagnosed as having metabolic syndrome[1] at baseline (52.9%) was reduced by half (25.8%) after treatment with ACOMPLIA™ 20 mg ($p<0.0001$ compared to placebo). Study findings for rimonabant 20 mg include:

- Waist circumference reduction of 9.1 cm (3.5 inches) in patients treated for a year (completers) with rimonabant 20 mg ($p<0.001$ vs. placebo).
- Average increase of 23% in HDL-cholesterol in completers ($p<0.001$ vs. placebo).
- Average reduction of 15% in triglycerides in completers ($p<0.001$ vs. placebo)
- A positive shift in LDL particle size, with a reduction ($p=0.002$ vs. placebo) in the proportion of smaller dense atherogenic LDL particles, which are associated with cardiovascular risk, and an increase ($p<0.001$ vs. placebo) in the proportion of larger, less atherogenic LDL particles.
- In a sub-group of patients adiponectin and leptin levels were measured. After one year of treatment, a significant increase of adiponectin level from baseline was found in the rimonabant 20 mg group vs. placebo ($p=0.001$). A significant decrease of leptin level from baseline was shown in the rimonabant 20 mg group compared to placebo ($p<0.001$) after one year of treatment.
- C Reactive Protein (CRP), an important inflammatory marker predictive of cardiovascular risk, was reduced by 27% in the rimonabant 20 mg group vs. an 11% reduction in the placebo group ($p<0.01$).
- Improved insulin sensitivity as demonstrated by glycaemic and insulin response during an Oral Glucose Tolerance Test. Over the 2 hour test, patients metabolized glucose more efficiently with rimonabant 20 mg compared to placebo. Blood glucose was reduced by 9% vs. baseline

[1] Metabolic Syndrome describes a collection of health risks or conditions that increase a person's chance to developing heart disease, stroke and diabetes. These conditions share the following characteristics as defined by the ATP III definition. At least 3 among these criteria: abdominal obesity: waist circumference Men > 102 cm (40 inches), Women 88 cm (35 inches); hypertension: ≥130/85 mmHg; Hypertriglyceridemia: ≥150 mg/dl; Low HDL cholesterol: Men <40 mg/dl, Women < 50mg/dl; Abnormal fasting glucose: ≥ 110 mg/dl.

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with rimonabant 20 mg compared to a 4% reduction in the placebo group ($p<0.001$), and their bodies had to produce less insulin to achieve this better glucose control (insulin levels reduced by 22% vs. baseline with rimonabant 20 mg compared to a 2% increase in the placebo group, $p<0.001$).

- In this study ACOMPLIA™ was well tolerated in this patient population. The most frequent side effects, mainly mild and transient, were nausea (3.2%, 7.2% and 12.7% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively) and dizziness (6.7%, 8.4% and 10.4% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively). Importantly the study raised no cardiovascular safety concerns for rimonabant and no difference was observed in the three groups with regard to depression and anxiety scores as measured by the Hospital Anxiety and Depression (HAD) scale. Drop-out rates due to side effects were 7% for placebo, 8.4% for rimonabant 5 mg and 15% for rimonabant 20 mg. No difference in overall drop-out rates were observed between the three groups (37.6%, 39.9% and 36.3% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively).

"In this study Rimonabant was effective in reducing abdominal obesity, which is now known to be a major independent risk factor for cardiovascular disease," said Jean-Pierre Després, principal investigator for RIO-Lipids and Professor in the Department of Food Sciences and Nutrition and Medicine at Laval University, and Director of Research at the Quebec Heart Institute located at the Laval Hospital Center in Quebec City, Canada. "While the weight loss seen was clinically relevant, what is truly remarkable in this study was the significant effect that rimonabant had on improving associated cardiovascular risk factors such as waist circumference, and glucose and lipid profiles."

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STRATUS-US Study Findings

STRATUS-US enrolled 787 smokers in a double-blind, placebo-controlled study, conducted in 11 clinical trial sites throughout the United States. Patients enrolled in the study smoked 23 cigarettes/day on average, were motivated to quit, and had, previously failed to quit on an average of four prior attempts. Patients were randomly assigned into one of three treatment groups (ACOMPLIA™ 5 mg or 20 mg or placebo) with weekly counseling.

Patients were treated for 10 weeks. During the first two weeks of the study, patients were allowed to smoke while initiating treatment but were given a target quit date at day 15. Abstinence from tobacco during the last four weeks of the 10 week treatment was reported by subjects and confirmed by carbon monoxide concentrations in expired air (≤10 ppm) and by plasma cotinine levels the principal nicotine metabolite (≤ 8 µg/L).

Study results showed that rimonabant 20 mg doubled the odds of quitting vs. placebo (p=0.002). 36.2% of patients treated with ACOMPLIA™ 20 mg and having completed the study quit smoking when compared with 20.6% of patients treated with placebo. 20.2% of patients treated with ACOMPLIA™ 5 mg quit smoking. On average patients lost 0.3 kg (just over half a pound) on ACOMPLIA™ 20 mg vs. a 1.1kg (2.4 lb) weight gain for patients on placebo (p<0.001). While those patients who were overweight or obese lost weight when treated with rimonabant 20 mg, normal weight patients did not.

In this study ACOMPLIA™ was well tolerated in this patient population. The most frequent side effects, mainly mild and transient, were nausea (9.2%, 8.8% and 15.7% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively) and upper respiratory tract infections (5.7%, 11.1% and 10% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively). Importantly the study raised no cardiovascular safety concerns for rimonabant and no differences were observed in the three groups with

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regard to depression and anxiety scores as measured by the Hospital Anxiety and Depression (HAD) scale. Drop-outs due to side effects were 3.8%, 5.7% and 6.9% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively. There was no difference in the overall drop-out rate between the rimonabant and placebo groups (27.9%, 31.2% and 28.2% for placebo, rimonabant 5 mg and rimonabant 20 mg respectively).

"Smoking is one of the leading modifiable risk factors for heart disease and we have very few medications available to help people stop smoking," said Robert Anthenelli, M.D., principal investigator of the STRATUS-US trial and associate Professor of Psychiatry at the University of Cincinnati College of Medicine. "STRATUS-US suggests that rimonabant may have a distinctive dual effect that could prove to be critical in helping patients to quit smoking while reducing the likelihood of weight gain."

ACOMPLIA™ (rimonabant) Clinical Development Program

The Phase III program on ACOMPLIA™ includes seven clinical trials that are part of two clinical development programs. The RIO (**R**imonabant **I**n **O**besity) Program has enrolled over 6,600 overweight/obese patients worldwide in four clinical trials designed to explore the role of ACOMPLIA™ in obesity management – weight loss/weight maintenance; prevention of weight regain after prior weight loss; and improvement of obesity-related risk factors such as diabetes and dyslipidemia. RIO-North America and RIO-Europe are two-year studies. RIO-Lipids and RIO-Diabetes are one-year studies.

The STRATUS (**ST**udies with **R**imonabant **A**nd **T**obacco **US**e) Program has enrolled over 6,500 patients in three Phase III trials worldwide. The studies are designed to explore the role of ACOMPLIA™ in smoking cessation and long-term abstinence and prevention of weight gain upon

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smoking cessation. STRATUS-US and STRATUS-EU are 10-week studies with a 42-week follow-up off treatment. STRATUS-WW is a one-year study with a one-year follow-up off treatment.

Rimonabant phase III programs in obesity and smoking cessation are due to be completed at the end of 2004; the product is yet non-approved for marketing.

Forward-Looking Statements

This press release contains statements that constitute forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. Forward-Looking statements are statements that are not historical facts. These statements include financial projections and estimates and their underlying assumptions, statements regarding plans, objectives and expectations with respect to future operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words "expect," "anticipates," "believes," "intends," "estimates" and similar expressions. Although Sanofi-Synthélabo's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi-Synthélabo, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. The following factors, among other risks and uncertainties that are described in our Form 20-F as filed with the SEC on June 25, 2003 and in the Reference Document filed with the French Commission des Opérations de Bourse (now the Autorité des Marchés Financiers) on April 23, 2003, could cause actual results to differ materially from those described in the forward-looking statements: the ability of Sanofi-Synthélabo to expand its presence profitably in the United States; the success of Sanofi-Synthélabo's research and development programs; the ability of Sanofi-Synthélabo to protect its intellectual property rights; and the risks associated with reimbursement of health care costs and pricing reforms, particularly in the United States and Europe. Sanofi-Synthélabo does not undertake any obligation to provide updates or to revise any forward-looking statements.

Investors and security holders may obtain a free copy of the Form 20-F and any other documents filed by Sanofi-Synthélabo with the SEC at www.sec.gov as well as of the Reference Document filed with the French Autorité des Marchés Financiers at www.amf-france.org or directly from Sanofi-Synthélabo on our web site at: www.sanofi-synthelabo.com.

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