Corporate Communications

Paris, november 9, 2004

Dear Madam, Dear Sir:

Please find herewith the press release issued today by the Steering Committee on the results of the RIO-North America trial during the American Heart Association meeting in New Orleans.

We remind you that sanofi-aventis will host a conference call today at 7:30 p.m. Paris time, 1:30 p.m. NY time
to comment on the RIO-North America study results presented today.

The phone number's are as follows:
France: 01 70 99 35 06
UK: 0845 301 40 25
USA: 1 866 308 2653
Rest of the world: + 44 208 322 3179

Password: sanofi-aventis

The slides will be webcasted on www.sanofi-aventis.com during the conference call but will not be available for download.

An audio replay will be available for 7 days (from today at 10:30 p.m. Paris time / 4:30 p.m. New York time).

In order to access to the replay please dial the following numbers:
UK : 0207 081 9440
USA : 1 800 8977 608
Password: 198050

Best regards,

Jean-Marc Podvin
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Xavier Pi-Sunyer, M.D.
Principal Investigator
RIO-North America
On behalf of the RIO Steering Committee

Press Announcement

LONG-TERM BENEFITS OF RIMONABANT CONFIRMED IN TWO-YEAR STUDY

Results from RIO-North America trial show that first year improvements in cardiovascular risk factors maintained in the second year of treatment

New Orleans, November 9, 2004 – The results of a two-year Phase III study in 3040 patients with rimonabant (Acomplia™), the first in a new class of therapeutic agents called selective CB1 Blockers, demonstrate that the benefits achieved with rimonabant 20mg at the end of the first year of the study were sustained in the second year of therapy with a good safety and tolerability profile vs. placebo. The two year results of the RIO-North America (**R**imonabant **I**n **O**besity) trial were presented for the first time today by Xavier Pi-Sunyer, M.D., Chief of the Division of Endocrinology, Saint Luke's – Roosevelt Hospital Center, Columbia University, New York and principal investigator of the study to the scientific community at the American Heart Association (AHA) Scientific Sessions in New Orleans, Louisiana. Patients treated with rimonabant 20mg for two years experienced a reduction in body weight and in waist circumference, demonstrating a significant reduction in abdominal fat, a key marker for cardiovascular disease. Patients treated with rimonabant 20mg over the two year period also achieved a significant increase in HDL-cholesterol (good cholesterol), a reduction in triglycerides and an improvement in insulin sensitivity.

The RIO-North America study is the largest of all rimonabant studies presented to date. The results from this study data are consistent with the findings from two previous large-scale studies on rimonabant – RIO-Lipids and RIO-Europe – communicated earlier this year and add to the ever-growing body of evidence supporting the drug's efficacy and tolerability profile. Rimonabant is currently being developed for the management of cardiovascular risk factors including reduction of abdominal obesity improving lipid and glucose metabolism, and as an aid to smoking cessation.

Obesity is a major public health burden and one of the most frequent causes of death worldwide mainly through cardiovascular disease. Obesity is typically measured by body mass index (BMI). However, recent findings have shown that visceral (abdominal) fat (simply measured by waist circumference) is a better predictor for heart attack than weight or BMI.[1] 44% of adult Americans have a waist circumference size exceeding the at-risk level (40 inches for men and 35 inches for women).[2] Visceral fat is associated with the cause of metabolic risk factors such as dyslipidemia or insulin resistance that may lead to diabetes, heart attack, stroke and other cardiovascular disease. Reducing abdominal fat is a recognized priority for preventing cardiovascular disease.[3]

"As the cardiovascular risk factors associated with obesity have become more manifest, it has become increasingly apparent that current approaches are insufficient. Excess abdominal fat in particular is increasingly recognized as one of the most telling harbingers of future cardiovascular complications," said Professor Pi-Sunyer. "The two-year results of the RIO-North America trial confirm that rimonabant is an innovative and promising tool for the long-term management of weight and associated cardiovascular risk factors in abdominally obese patients," he added.

RIO-North America objectives and design

RIO-North America was a phase III, multinational multicenter, randomized, double-blind, placebo-controlled trial comparing two fixed-dose regimens of rimonabant (5mg and 20mg once daily) to placebo for a period of two years. The study was conducted on 3,040 patients at 72 centers in the U.S. and Canada.

The objectives of the trial were to assess the effect of rimonabant on weight loss over a period of one year and to determine the ability of rimonabant to prevent weight regain during a second year of treatment. The study objectives also included an assessment of improvement in risk factors associated with abdominal obesity (as measured by waist circumference) such as dyslipidemia, glucose metabolism, and the metabolic syndrome, and an evaluation of the safety and tolerability of rimonabant over a period of two years.

After a screening period of one week, patients were prescribed a mild hypocaloric diet (designed to reduce daily caloric intake by 600 kcal from the patients' energy requirements) and entered a four-week single-blind placebo run-in period. Afterward, patients were randomly allocated to one of the three treatment groups: placebo or rimonabant 5mg or 20mg for 52 weeks of double-blind treatment using a randomization ratio of 1:2:2.

After the first year of treatment, patients who received rimonabant 5mg or 20mg were re-randomized to either the same dose of rimonabant or placebo using a randomization ratio of 1:1 for an additional 52-week treatment period (the placebo group remained on placebo during the second year).

Rio-North America findings

The findings presented today show that two-year treatment with rimonabant 20mg significantly lowered weight, reduced abdominal fat, diminished cardiovascular risk factors and decreased metabolic disorders in this patient population. At two years waist circumference, a simple measure of abdominal fat, in patients treated with rimonabant 20mg for the full two year period was reduced by 8 cm (3.1 inches) versus 4.9 cm (1.9 inches) for rimonabant 5 mg and 3.8 cm (1.5 inches) in the placebo group ($p<0.001$). 62.5% of patients who received treatment with rimonabant 20mg throughout the two year period lost more than 5 percent of their initial body weight versus 36.7% of those on rimonabant 5mg and 33.2% of those on placebo ($p<0.001$). In the same period, 32.8% of patients treated with rimonabant 20mg lost in excess of ten percent of their initial body weight, versus 20% of those on rimonabant 5mg and 16.4% of patients on placebo ($p<0.001$).

Metabolic parameters were also significantly improved in patients treated with rimonabant 20 mg throughout the two year period with HDL-cholesterol increased by 24.5% in the rimonabant 20mg group versus 15.6% and 13.8% in the rimonabant 5 mg and placebo groups respectively ($p<0.001$). Triglycerides were reduced by 9.9% in patients treated with rimonabant 20mg throughout the two year period versus 5.9% and 1.6% in the rimonabant 5mg and placebo groups respectively ($p<0.05$).
Although diabetic patients were not included in the study, patients on rimonabant 20mg had significantly improved their insulin sensitivity compared to those on rimonabant 5mg and on placebo.

The effect of rimonabant on HDL-cholesterol, triglycerides, fasting insulin and insulin sensitivity (as measured by HOMA) appeared to be twice that which would be expected from the degree of weight-loss achieved (all $p<0.05$)

Of particular note is that the number of patients diagnosed with metabolic syndrome at baseline and treated with rimonabant 20mg over the two year study period was reduced by more than one third ($p<0.001$). Metabolic syndrome encompasses a series of serious health risks or conditions that increase a person's chance to develop heart disease, stroke and diabetes.

A good safety and tolerability profile

Rimonabant 20mg proved to be safe and tolerable vs. placebo throughout the two year study period. Side effects were mainly minor and short-lived. Overall discontinuation rates for adverse events in the first year of the study were 7.2%, 9.4% and 12.8% in placebo, rimonabant 5mg and rimonabant 20mg groups. The discontinuation rates for patients randomly assigned to continue their first-year treatment for a second year were 6.7%, 8.3% and 6.0% in placebo, rimonabant 5mg and 20mg groups. No differences were noted in the three groups with regards to scores measured by the Hospital Anxiety Depression scale. In this trial and in two preceding studies, Rimonabant was also shown to have no significant EKG or heart rate changes.

Rimonabant and the EC system

The EC System is a newly discovered, physiological system in the body that is believed to play a key role in the central and peripheral regulation of energy balance, glucose and lipid metabolism as well as in the control of tobacco dependence.

CB_1 receptors are found in the brain as well as in peripheral tissues of the body such as adipocytes (or "fat cells") which are associated with lipid and glucose metabolism. Excessive food intake or chronic tobacco use result in an overactive EC system. This can trigger a cycle of increased eating and fat storage, or, in the case of smoking, sustained tobacco dependence.

Rimonabant is the first in a new class of drugs called cannabinoid type 1 (CB_1) blockers. By selectively blocking both centrally and peripherally the CB_1 receptors, rimonabant modulates the overactive EC System. The results have been seen in reducing cardiovascular risk factors through reduction in abdominal fat and a corresponding improvement in metabolic parameters that is beyond that expected through weight reduction.

The new clinical results from the RIO-North America study further suggest that rimonabant may become an important tool in the cardiovascular risk factor reduction armamentarium.

References

1. Yusuf et al, Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*, Volume 364 Number 9438 September 11–17, 2004
2. Ford et al, Increasing Prevalence of the Metabolic Syndrome Among US Adults. *Diabetes Care*, Vol 27, Number 10, October 2004
3. Domanski M, Proschan M. The Metabolic Syndrome. *Journal of the American College of Cardiology*, 2004, 43, May 2000

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