



## MEDIA

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# **Plavix<sup>®</sup> Plus Aspirin More Effective than Aspirin Alone in Preventing Major Vascular Events in Patients with Atrial Fibrillation Who Cannot Take Oral Anticoagulants**

**- Greatest Benefit Seen in Reducing Stroke, the Highest Risk  
for Atrial Fibrillation Patients -**

**Paris, France and Princeton, New Jersey - March 31, 2009** - Sanofi-aventis (EURONEXT: SAN and NYSE: SNY) and Bristol-Myers Squibb Company (NYSE: BMY) announced today new findings from a landmark investigational study that demonstrated that, for patients with atrial fibrillation who were at increased risk for stroke and could not take an oral anticoagulant (OAC) medication, taking Plavix<sup>®</sup> (clopidogrel bisulfate) in addition to aspirin significantly reduced major vascular events by 11% over aspirin alone, at a median of 3.6 years of follow-up (6.8% vs. 7.6% per year, p=0.01).

The greatest benefit was seen in the reduction of stroke, by 28% (2.4% vs. 3.3% per year, p<0.001), which is the primary goal of physicians treating patients with atrial fibrillation. Other components of major vascular events -- non-CNS systemic embolism (a blood clot in the bloodstream but not in the brain), heart attack or vascular death -- did not reach statistical significance.

Compared to aspirin alone, taking Plavix<sup>®</sup> in addition to aspirin significantly and as expected increased the rate of major bleeding (2.0% vs. 1.3% per year, RR=1.57, p < 0.001). The study results, from the trial called **ACTIVE-A**, were presented today at a late-breaking session during the 58<sup>th</sup> Annual Scientific Session of the American College of Cardiology.

*“For patients with atrial fibrillation who are at increased risk for stroke but cannot take oral anticoagulants, these findings suggest a potential change in clinical practice,”* said ACTIVE-A principal investigator Stuart Connolly, MD, Department of Medicine, McMaster University, Hamilton, Ontario, Canada. *“Stroke is a major concern since it results in significant morbidity and mortality.”*

In atrial fibrillation (AF), the most common heart arrhythmia, blood can pool in the upper chambers of the heart (the atria) and form clots, which can be released into the bloodstream and cause a vascular event. With a five-fold greater risk for stroke, AF patients account for about 15% of all strokes. Thus, in addition to therapies to normalize heart rhythm, treatment guidelines recommend AF patients at moderate-to-high risk for stroke also receive OAC therapy, which is effective in preventing vascular events in these patients. However, there are many patients who cannot take OACs or cannot maintain their blood coagulation inhibition within the narrow therapeutic range required to reduce the risk of vascular events without increasing the risk of life-threatening bleeding complications such as intracranial hemorrhage. Studies show that less than half of AF patients overall use OACs.

*“Sanofi-aventis and Bristol-Myers Squibb Company sponsored ACTIVE-A as part of our ongoing commitment to investigate the full potential of Plavix<sup>®</sup> through major clinical trials, covering a broad spectrum of patients at risk of cardiovascular events early and long-term,”* said Brian Daniels, Senior Vice President, Global Development and Medical Affairs, Bristol-Myers Squibb.

*“These results are of major interest for people with atrial fibrillation and at increased risk for vascular events, particularly stroke, who cannot take OACs,”* said Jean-Pierre Lehner, Chief Medical Officer, sanofi-aventis.

### **Study and Findings**

ACTIVE-A was a Phase III, double-blind, placebo-controlled trial designed to compare the combination of Plavix<sup>®</sup> 75mg once daily plus aspirin (75-100mg daily recommended dose) to aspirin alone (75-100mg daily recommended dose) for preventing the first occurrence of a major vascular event, the primary endpoint, during the trial, with a median of 3.6 years of follow-up. Major vascular events included stroke, non-central nervous system (non-CNS) systemic embolism, heart attack, or vascular death. The trial included 7554 patients with atrial fibrillation who could not take OACs and had at least one major risk factor for stroke (risk factors included: 75 years of age or older; on treatment for systemic hypertension; prior stroke, transient ischemic attack, or non-CNS systemic embolus; left ventricular dysfunction; documented peripheral vascular disease; and age 55 to 74 years with either diabetes requiring drug therapy or with documented previous heart attack or coronary artery disease). Patients were determined unsuitable for OAC by the physician for the following reasons: specific risk of bleeding, physician judgment that OACs were inappropriate for the patient, or the patient's desire to avoid OAC therapy.

Plavix<sup>®</sup> plus aspirin therapy compared to aspirin alone, respectively, also resulted in:

- A non-statistically significant reduction in heart attacks of 22% (0.7% vs. 0.9% per year, p=0.08)
- No statistically significant reductions in the other components of the primary endpoint, including non-CNS systemic embolism (0.4% vs. 0.4% per year, RR=0.96, p=0.84), vascular death (4.7% vs. 4.7% per year, RR=1.00, p=0.97), or total death (6.4% vs. 6.6% per year, RR=0.98, p=0.69)
- Statistically significant increases, as expected, in the rate of major bleeding (2.0% vs. 1.3% per year, RR=1.57, p<0.001) and intracranial hemorrhage (0.4% vs. 0.2% per year, RR=1.87,

p=0.006), but non-significant increases in fatal bleeding (0.3% vs. 0.2% per year, RR=1.56, p=0.07) and hemorrhagic stroke (0.2% vs. 0.2% per year, RR=1.37, p=NS)

### About the ACTIVE Trial

ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) is a comprehensive program which is composed of three trials: ACTIVE-W, ACTIVE-A and ACTIVE-I. ACTIVE-A and ACTIVE-W started as two parallel trials, and the decision about which trial to enroll each patient in was made by the investigators.

ACTIVE-W was stopped early after an interim analysis demonstrated that for atrial fibrillation patients who can take an OAC, OAC therapy produced a greater reduction of vascular events (stroke, non-CNS systemic embolism, heart attack, or vascular death) than Plavix<sup>®</sup> plus aspirin. There were no statistically significant differences in major bleeding between the two groups; however, there were significantly more minor bleeds with Plavix<sup>®</sup> plus aspirin compared with OAC.

The ACTIVE-W findings are consistent with the current standard of care and reaffirm the important role of well-controlled OAC therapy in this patient population, and are specific to patients with atrial fibrillation who can take an OAC.

ACTIVE-A specifically addressed the efficacy and safety of dual antiplatelet therapy (Plavix<sup>®</sup> plus aspirin) versus aspirin alone in patients with atrial fibrillation who were at increased risk for stroke and could not take an OAC.

ACTIVE-I, a trial of irbesartan in patients participating in ACTIVE-A or ACTIVE-W who do not require an angiotensin receptor–blocking agent, is ongoing.

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### About Plavix<sup>®</sup>

Plavix<sup>®</sup> is recommended daily for patients who have had a recent heart attack or stroke, or poor circulation in the legs that may cause pain during exercise, such as walking, and may be relieved by rest (known as peripheral artery disease, or P.A.D.). Plavix<sup>®</sup> is also recommended in addition to aspirin for patients who have been hospitalized with heart-related chest pain (unstable angina) or had a heart attack.

### Important Risk Information

- Plavix<sup>®</sup> is contraindicated in patients with active pathologic bleeding such as peptic ulcer or intracranial hemorrhage. Plavix<sup>®</sup> should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or coadministration with NSAIDs or warfarin. **(See CONTRAINDICATIONS and PRECAUTIONS.)\***
- The rates of major and minor bleeding were higher in patients treated with Plavix<sup>®</sup> plus aspirin compared with placebo plus aspirin in clinical trials. **(See ADVERSE REACTIONS.)\***
- As part of the worldwide post marketing experience with Plavix<sup>®</sup>, there have been cases of reported thrombotic thrombocytopenic purpura (TTP), some with fatal outcome. TTP has been reported rarely following use of Plavix<sup>®</sup>, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). **(See WARNINGS.)\***
- In clinical trials, the most common clinically important side effects were pruritus, purpura, diarrhea, and rash; infrequent events included intracranial hemorrhage (0.4%) and severe neutropenia (0.05%). **(See ADVERSE REACTIONS.)\***

\*Please see full prescribing information for the United States by visiting [www.plavix.com](http://www.plavix.com). For the always most updated Plavix<sup>®</sup> labelling information in Europe please refer to: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/H-174-PI-en.pdf>.

**About Atrial Fibrillation**

The most common form of heart arrhythmia, atrial fibrillation is estimated to affect a combined total of more than 7.5 million people in the United States, European Union and Japan (2.3 million, 4.5 million and 729,000, respectively). AF is an abnormal heart rhythm in which the heart's two upper chambers (the atria) contract fast and irregularly. As a result, blood can pool in the atria and can form clots. If a clot is released into the bloodstream, it can cause a stroke or other vascular event. Thus, AF increases the risk of stroke up to five-fold, worsens the prognosis of patients with cardiovascular risk factors, and doubles the risk of mortality. AF may occur rarely or occasionally, or it may become a persistent heart arrhythmia lasting for years.

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**CONFERENCE CALL**

A conference call on the results of the ACTIVE-A study will be organized by sanofi-aventis today: ***March 31, 2009 at 5:30 PM Paris time / 4:30 PM London / 11:30 AM New York.***

It will be hosted by:

**Jean-Pierre Lehner, M.D., Senior Vice-President, Chief Medical Officer**

**Pierre Chancel, Senior Vice-President, Global Marketing & Access**

The conference call will be available in audio-only mode on our website: <http://www.sanofi-aventis.com>

***AUDIO REPLAY***

The replay will be available approximately 2 hours after the end of the call and through April 14, 2009.

France	+33 (0) 1 72 28 01 49
UK	+44 (0) 20 7075 3214
USA	+1 866 828 2261
Access code	285917#

**About sanofi-aventis**

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY). For more information, please visit:

[www.sanofi-aventis.com](http://www.sanofi-aventis.com).

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life. For more information, visit [www.bms.com](http://www.bms.com).

**Statement on Cautionary Factors****Sanofi-aventis**

*This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include product development, product potential projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future events, operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words “expects,” “anticipates,” “believes,” “intends,” “estimates,” “plans” and similar expressions. Although sanofi-aventis’ 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-aventis, 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. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMEA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such products candidates, the absence of guarantee that the products candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives as well as those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under “Risk Factors” and “Cautionary Statement Regarding Forward-Looking Statements” in sanofi-aventis’ annual report on Form 20-F for the year ended December 31, 2008. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.*

**Bristol-Myers Squibb**

*This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995, regarding the research, development and commercialization of products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the clinical trials described in this release will support a regulatory filing. Forward-looking statements in the press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2008, its Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise.*