Dronedarone (Multaq®) Reduced the Incidence and Duration of Hospitalization in Patients with Atrial Fibrillation

- New post-hoc analysis from Athena Study showed that Multaq® on top of standard therapy significantly decreased the total number of hospital days by 28% in patients with atrial fibrillation or flutter -

New Orleans, LA – November 11, 2008 – New data from the landmark ATHENA trial showed that dronedarone significantly reduced the incidence and total duration of hospital stays among patients with atrial fibrillation / atrial flutter (AF/AFL). This post-hoc analysis was presented at the *American Heart Association* Scientific Sessions 2008 in New Orleans, Louisiana.

In this new analysis, dronedarone significantly reduced the total number of hospital days by 28 percent ($p<0.001$) versus placebo (9,995 days vs. 13,986 days), and decreased by 35 percent ($p<0.001$) the total length of time spent in hospital for cardiovascular reasons (5,875 days vs. 9,073 days).

In addition to the demonstrated reduction of AF-related hospitalization by 37 percent ($p<0.001$), dronedarone reduced the incidence of first non-AF related CV hospitalization (e.g. myocardial infarction or unstable angina) by 14 percent ($p=0.016$). Dronedarone did not increase the incidence of non-cardiovascular hospitalizations in comparison to the placebo arm.

"*The incidence of AF-related hospital admissions has dramatically increased in recent years, and therapeutic solutions to reduce this burden are needed*," said Dr Christian Torp-Pedersen from the Gentofte University Hospital, Copenhagen, Denmark and a member of the steering committee of the ATHENA study. "*These new ATHENA data showed that for the first time, an anti-arrhythmic drug significantly and consistently reduced hospitalization incidence and duration, which led to a substantial reduction of total hospitalization burden in this patient population*."

A second post-hoc analysis from ATHENA, also presented during the AHA, confirmed the rhythm and rate controlling properties of dronedarone, already previously demonstrated in lower risk populations studied in the EURIDIS[1], ADONIS[1] and ERATO[2] trials. This analysis showed that dronedarone reduced the incidence of first AF recurrence by 25 percent in patients in sinus rhythm at study initiation ($p<0.001$), and the incidence of first electrical cardioversion by 31 percent ($p<0.001$), compared with placebo.

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Dronedarone also decreased mean heart rate during atrial fibrillation to 78 beats per minute, compared with 87 for placebo (p<0.001). Fewer patients developed permanent atrial fibrillation during the study in the dronedarone group – 178 patients (7.7%) compared with 295 patients (12.7%) in the placebo arm (p<0.001). In these patients, the non-significant reduction of CV hospitalization or death was 26% lower for those receiving dronedarone (p=0.096). These results are consistent with the overall study results.

"*This study demonstrates both significant rhythm and rate controlling properties of dronedarone in the ATHENA population, which consisted of higher-risk patients with atrial fibrillation*" added Dr. Richard Page, Professor and Head of the Division of Cardiology at the University of Washington School of Medicine, Seattle, USA and a member of the steering committee of the ATHENA study. *"It is intriguing that there was a trend toward reduction of the primary endpoint of cardiovascular hospitalization or death even in patients with permanent AF, suggesting that the benefit of dronedarone may not only be linked to arrhythmia control"* .

The most frequently reported adverse events of dronedarone vs. placebo in the ATHENA trial were gastrointestinal effects (26% vs. 22%), skin disorders (10% vs. 8%, mainly rash) and mild increase in blood creatinine (4.7% vs. 1%) due to inhibition of tubular secretion of creatinine in the kidneys. The mechanism of blood creatinine increase was well defined in a separate study of healthy volunteers and is not indicative of renal toxicity. In the ATHENA trial, compared to placebo, dronedarone showed a low risk of pro-arrhythmia and no excess of hospitalizations for congestive heart failure. There was a similar rate of study drug discontinuation between the 2 study groups.

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About Atrial Fibrillation

Atrial fibrillation (AF) is a common heart arrhythmia in which the upper chambers of the heart beat in an uncoordinated and disorganised fashion, which can cause palpitations, shortness of breath and fatigue. Atrial fibrillation (AF) currently represents a major economic burden for society.[3] 70 percent of the annual cost of AF management is driven by inpatient care and interventional procedures.[4] Hospitalizations for AF have increased dramatically (2- to 3-fold) in recent years.[5] AF hospitalizations now represent a third of all hospitalizations for arrhythmia and mortality. AF affects nearly seven million people in the European Union and the United States.[6]

The condition is increasingly frequent with advancing age and is often caused by age-related changes in the heart or as a result of cardiovascular disease. AF increases the risk of stroke five-fold and heart failure two- to three-fold. AF also doubles the risk of mortality and is an independent risk factor for sudden cardiac death.

Without appropriate management, AF can lead to serious complications such as stroke and congestive heart failure. In addition to preventing stroke and reducing the burden of the disease, successful management of AF should also aim at further reducing CV morbidity and mortality.[7]

The aims of treatment for patients with AF are related to managing the arrhythmia itself and to the prevention of thromboembolism (obstruction of a blood vessel caused by fragments of a blood clot carried from the site of origin to obstruct another vessel). Atrial fibrillation may be treated with medications which either slow the heart rate or revert the heart rhythm back to normal.

About the ATHENA Study

The landmark ATHENA study is the only double-blind, anti-arrhythmic, morbidity-mortality study in patients with AF. It was conducted in more than 550 sites in 37 countries and enrolled a total of 4,628 patients.

Previous results from the landmark ATHENA study have shown that dronedarone on top of standard therapy decreased the combined primary endpoint of cardiovascular hospitalization or death from any cause by a statistically significant 24 percent (p<0.001) as compared to placebo and reduced the risk of cardiovascular hospitalization by 25 percent (p<0.001). These results were achieved with a favorable safety profile.

The patients studied in ATHENA were either 75 years of age or older (with or without cardiovascular risk factor) either below 75 years of age with at least one additional cardiovascular risk factor (hypertension, diabetes, previous cerebrovascular event, left atrium size greater than 50 mm or left ventricular ejection fraction lower than 40 percent). Patients with decompensated heart failure (NYHA class IV) were excluded. Patients were randomized to receive dronedarone 400 mg BID or placebo, with a maximum follow-up of 30 months.

The ATHENA study objectives were to show a potential benefit of dronedarone on the primary composite endpoint of all-cause mortality combined with cardiovascular hospitalization as compared to placebo. The pre-specified secondary endpoints were death from any cause, cardiovascular death and hospitalisation for cardiovascular reasons. The pre-specified safety endpoint was the incidence of treatment emergent adverse events (between first study drug intake and last study drug intake plus 10 days) including: all adverse events, serious adverse events, adverse events leading to study drug discontinuation.

About dronedarone (Multaq®)

Dronedarone (Multaq®) is an investigational treatment and the only Anti-Arrhythmic Drug (AAD) to have shown a significant reduction in morbidity and mortality in AF/AFL patients with a favourable safety profile as evidenced by a low incidence of pro-arrhythmia (including torsades de pointes) and extra-cardiac organ toxicity. Dronedarone, discovered and developed by sanofi-aventis, has been studied in a clinical development program including more than 6,200 patients. Dronedarone is one of the major therapeutic innovations in atrial fibrillation for the last twenty years. Dronedarone (Multaq®) has been granted a priority review by the U.S. Food and Drug Administration (FDA) and a registration dossier is also under regulatory review by the European Medicines Agency (EMEA).

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).

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