

## PALLAS Trial

PALLAS (Permanent Atrial fibrillation outcome Study using Dronedarone on top of standard therapy) is a multinational, randomized, double-blind, parallel-group, placebo-controlled, multicenter Phase IIIb trial comparing the efficacy of Multaq® 400mg twice-daily with placebo in more than 10,000 patients with permanent atrial fibrillation (AF). Patient enrollment will begin in Q3 2010.<sup>1,2</sup>

### **PALLAS**

#### **Study Rationale**

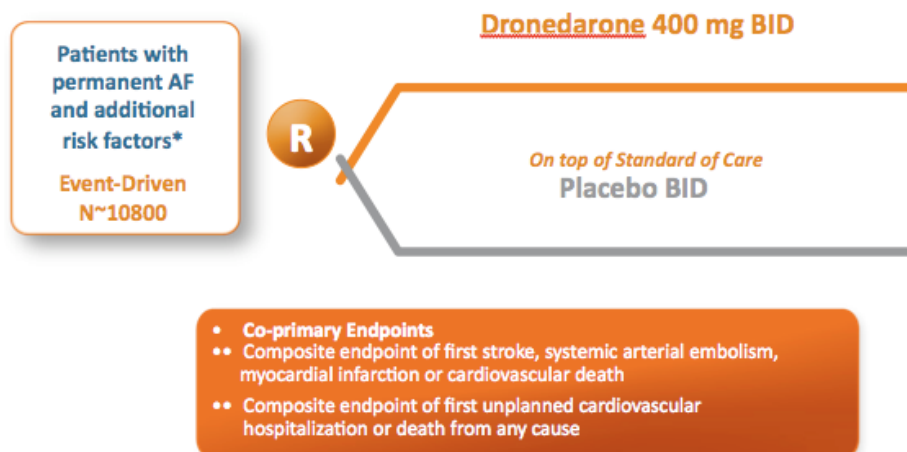
Approximately 50 percent of patients with AF have permanent AF,<sup>3,4</sup> which is associated with high rates of major adverse cardiovascular events.<sup>5</sup> No drug for arrhythmia has yet been shown in a large-scale clinical trial to reduce morbidity and mortality in this patient population.<sup>6</sup> A post-hoc analysis of the landmark ATHENA trial in patients who progressed to “permanent” AF and stayed in AF throughout the course of the study, showed a consistent trend towards a decrease in cardiovascular hospitalization or death for patients who received Multaq. This subgroup of patients behaved similarly to the overall study group in ATHENA. The finding implies that the outcomes seen in ATHENA may not be just a result of rhythm status.<sup>7</sup> PALLAS will prospectively assess the impact of Multaq on major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death), or cardiovascular hospitalization or death from any cause, among patients with permanent atrial fibrillation and additional risk factors.<sup>1</sup>

#### **Study Objectives**

- **Primary objective:**
  - Demonstrate a reduction among patients with permanent atrial fibrillation and additional risk factors in either or both of two composite outcomes which are
    - 1) Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death) or
    - 2) Cardiovascular hospitalization or death from any cause
- **Secondary objectives:**
  - The secondary objectives are to evaluate the efficacy of Multaq® in preventing cardiovascular death and whether the drug is well-tolerated in this patient population.<sup>1,2</sup>

#### **Study Design**

A multinational, randomized, double-blind, parallel-group, placebo-controlled, multicenter Phase IIIb trial comparing the efficacy of Multaq® 400mg twice-daily with placebo in permanent AF patients.



- **Treatment Protocol:**
  - All patients will receive standard treatment to control heart rate and prevent blood clots (antithrombotic therapy).
  - Patients will be randomized to receive additional treatment with either dronedarone at a dosage of 400 mg twice daily or placebo.
  
- **Eligibility:**
  - To participate patients must be: above 65 years of age with at least one of the following major risk factors:
    - systemic arterial embolism
    - myocardial infarction
    - documented coronary artery disease
    - prior stroke
    - symptomatic heart failure
  
  - Or, be above 75 years and suffering both from hypertension and diabetes mellitus.
  - Exclusion criteria include patients with New York Heart Association (NYHA) Class IV heart failure or recent unstable NYHA Class III heart failure.
  
- **Duration:** PALLAS is an event-driven trial with a fixed Common Study End Date, meaning that the study duration will depend upon the occurrence of a statistically required number of events. The duration for the last patient randomized must be not less than 3 months.<sup>2</sup>

#### ***Patient Enrollment***

- **Target Enrollment:** The trial will enroll approximately 10,800 eligible patients with permanent atrial fibrillation.
- **Site Locations:** Patients will be enrolled at 700 trial sites in 43 countries in Europe, North America, Asia, South America, Africa and Australia.
- **To Enroll:** Information will be available online when enrollment begins in Q3.

#### **PERMANENT ATRIAL FIBRILLATION**

- Atrial fibrillation (AF) is a serious, complex and progressive<sup>8</sup> disease in which the upper chambers of the heart beat in an uncoordinated and disorganized fashion, resulting in a very irregular and fast rhythm (i.e., an irregular heartbeat).
- According to ACC/AHA/ESC guidelines, permanent AF is the designation given to a long-standing AF in which cardioversion (medical intervention designed to restore sinus rhythm) has failed or has been foregone.<sup>9</sup>
- Major adverse events and death occur more often in patients with permanent AF compared with those with paroxysmal or persistent AF.<sup>10</sup>
- The incidence of atrial fibrillation is growing worldwide in relation to aging populations. It is emerging as a public health concern, affects about 4.5 million people in Europe and represents one-third of hospitalizations for arrhythmia in the European Union.<sup>6</sup>
- Atrial fibrillation leads to potential life-threatening complications. AF increases the risk of stroke up to five-fold<sup>5</sup>, worsens the prognosis of patients with cardiovascular risk factors,<sup>6,11</sup> and doubles the risk of mortality with significant burden on patients, health care providers and payers.<sup>6</sup>

#### **ABOUT MULTAQ®**

Multaq®, discovered and developed by sanofi-aventis, has been studied in a clinical development program, including seven international, multicenter, randomized clinical trials involving more than 7000 patients with almost 4000 patients receiving Multaq®. The landmark ATHENA trial was the largest anti-arrhythmic drug trial conducted in patients with AF/AFL, involving 4,628 patients with a follow-up of 30 months. In this trial, Multaq®, on top of standard cardiovascular therapy, significantly reduced cardiovascular hospitalization or

death by 24 percent ( $p < 0.001$ ) when compared to placebo, meeting the study's primary endpoint. This result was entirely attributable to a reduction in cardiovascular hospitalization.

Multaq® has a fixed dose regimen of twice daily 400 mg tablets to be taken with morning and evening meals. Treatment with Multaq® does not require a loading dose and can be initiated in an outpatient setting. Most common adverse reactions are diarrhea, nausea, vomiting, abdominal pain, asthenia (weakness) and skin rash.

The European Commission granted marketing authorization for Multaq® in November 2009. Multaq® is indicated in the EU in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. The use of Multaq® in unstable patients with NYHA class III and IV heart failure is contraindicated. Because of limited experience in stable patients with recent (1 to 3 months) NYHA class III heart failure or with Left Ventricular Ejection Fraction (LVEF)  $< 35\%$ , the use of Multaq® is not recommended in these patients.<sup>12</sup>

In the U.S., Multaq® is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age  $> 70$ , hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or left ventricular ejection fraction [LVEF]  $< 40\%$ ), who are in sinus rhythm or who will be cardioverted.<sup>13</sup>

Multaq® is currently available in the U.S., Canada, U.K., Switzerland, Germany, Denmark, Ireland, Norway and Finland and is being launched in most European countries in 2010.

- 
- 1 Pallas. A new outcomes trial with Multaq presentation. 4.14.10.
  - 2 Trial information will be available in the near future via <http://www.clinicaltrials.gov/>
  - 3 Levy, S Maarek M, Coumel P, et al., Characterisation of different subsets of atrial fibrillation in general practice in France: the ALFA study, *Circulation*, 1999;99:3028-35.
  - 4 EU Intention to Rx study (Dec.08); US ATU Tracking (June 09)
  - 5 Lloyd-Jones et al. Lifetime Risk for Development of Atrial Fibrillation: The Framingham Heart Study. *Circulation*. 2004; 110:1042-1046.
  - 6 Hohnloser SH et al. *N Engl J Med* 2009;360:668-78.
  - 7 Page R, et al. Abstract 4097: Rhythm- and Rate-Controlling Effects of Dronedaron in Patients with Atrial Fibrillation: Insights From the ATHENA Trial. *Circulation*. 2008;118:S\_827.
  - 8 Van Gelder I et al. The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm. *Europace*. 2006; 8: 943–949.
  - 9 Fuster V et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *European Heart Journal* (2006) 27, 1979-2030.
  - 10 Nieuwlaat R, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on Atrial Fibrillation. *European Heart Journal* (2008) 29, 1181–1189.
  - 11 Wachtell, K, Lehto, M, Gerds, E. Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol. *Journal of the American College of Cardiology*. 2005; 45:712-719.
  - 12 European Medicines Agency. European Public Assessment Report. Doc. Ref.: EMA/625172/2009; EMEA/H/C/1043
  - 13 MULTAQ U.S. Prescribing information <http://products.sanofi-aventis.us/Multaq/Multaq.pdf>